BODY FLUIDS IN SURGERY

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PREFACE TO SECOND EDITION

In this new edition every chapter has been extensively revised, much new material has been incorporated and a number of new diagrams have been added The descriptions of "acid base" balance, acidosis and alkalosis have been very largely rewritten and combined in a new chapter on the maintenance of chemical neutrality in the body For what seems to be the first time in a book of this kind the Bronsted Lowry convention has been used in the discussion of acid base equilibrium in the hope that the use of this simpler terminology will make the subject less confusing the eventual adoption of this convention is as certain now as that of milliequivalents was fifteen years ago and will no doubt be as strongly resisted.

Since more major surgery is done in those hot countries where the bulk of the world population is found the effects of hot and humid climates on the distribution of water and minerals in the body become increasingly important to the surgeon At present very little is known of such effects in various races but as much as possible has been included in appropriate sections of this edition.

The section on the effects of injury also has been almost completely rewritten and enlarged and now includes discussions of the effects of starvation and of the hormonic basis of the bodily reaction to injury

Recent rapid increases in the range and scope of surgical operations to relieve gross abnormalities of the alimentary tract in newborn babies have shown that much of the ultimate success of such operations depends on the post-operative care which is provided Our knowledge of the physiology of the newborn child is meagre and post-operative treatment has so far been largely empirical and scaled down from the orthodox treatment provided for adults As more is learned of neonatal functions after operation during the first week of life it is becoming evident that estimation of neonatal requirements in this way is unsatisfactory and that more direct measurements are needed. In a new chapter an account is given of present knowledge of the important variations

in composition and function in the infant and their bearing on post-operative management.

My debt to others has increased and from a number of colleagues I have had the benefit of comments and advice during discussions which often took root unnoticed and is difficult to acknowledge; in particular Professor Moncrieff, Dr. Barbara Clayton and Dr. A. H. Snaith have read sections and made valuable suggestions. I wish to acknowledge also the kindness of the Editor of the *Lancet* in allowing me to reproduce Figs 5, 6, 8, 9, and 10.

Once again I am indebted to Mr. Macmillan and his staff for their continued help and for their expeditious and efficient handling of the production of this book.

LONDON, 1960. A. W. W

PREFACE TO FIRST EDITION

There are few short cuts or routine answers for the surgeon who has to solve the problems set by the patient who has suffered large losses of body fluids. His therapeutic decisions must be based on a knowledge of normal body composition an accurate and detailed history of the illness and fluid loss of the individual patient and an understanding of the effects these disturbances will have on structure and function Although previous experience will modify his interpretation of the clinical features and the treatment he adopts, the deeper his understanding of the physiology of the body fluids the closer will such treatment approach the ideal There seems to be a need not only for advice in the management of the common disturbances of equilibrium in the composition and distribution of the body fluids, but also for a set of simple rules on which to base a routine of treatment in all sorts, sizes and conditions of patients Such a set of rules does not exist, to make allowances for individual variations within the so-called limits of normal of sex, age, stature and nutritional state is difficult if not impossible in a universal scheme of diagnosis and treatment. Moreover, the speed and chemical delicacy of the complicated inter-related compensatory reactions which follow the loss of body fluids of any kind are perhaps too little appreciated by most clinicians in their search for therapeutic simplicity

In this book an attempt has been made to provide in a convenient form, first, sufficient information for a basic understanding of the behaviour of the body fluids in health and disease, and secondly an account of the management of the disturbances of the body fluids which occur in surgical patients. It has been written primarily for those responsible for the care of surgical patients in the belief that the detailed management of disturbances of fluid balance in his patients rightly remains the responsibility of the surgeon

Until about 1939 our knowledge of the physiology of the body fluids was almost confined to measurements by chemical methods of concentration of substances dissolved in plasma and extra-

and ionic distribution, does not give any idea of the dynamic existence of minerals and water in the body

In this book emphasis has been placed on the clinical as opposed to the laboratory approach to the patient. Even the most complete laboratory data at present obtainable will give only a limited understanding of the state of the patient at a particular moment Repeated visits to the bedside at regular intervals do not cost the patient any blood or discomfort and are commonly more rewarding than the perusal of reports of biochemical estimation of the composition of his body fluids. The hardest thinking must be done before any blood is withdrawn for chemical examination, and the examination of this blood should be planned to show if possible whether the clinical diagnosis is right or wrong This is not to say that biochemical estimations are not of value in clinical surgical practice. Only by the continued application of the scientific method of measurement to the study of surgical problems can any improvement in our present state of ignorance be expected As a spur to assiduous study at the bedside and in the laboratory a proper sense of humility is required against the background of lack of knowledge and imperfect understanding of the behaviour of the body in normal and diseased conditions.

To keep this book reasonably short much material and many references have been excluded which would have had places in a comprehensive review of this subject. Nevertheless sufficient references are given to provide an ample introduction to the original work. Most writers are more or less deeply impregnated with and indebted to the work of those who have preceded them, in this field the debt to Gamble Coller, Moyer, Darrow, Cuthbertson, Marriott and McCance, to mention only a few of the pioneers, is heavy and will endure. To my chiefs, the late Sir John Fraser, Sir James Learmonth and Professor W C Wilson my debt is a more personal one. To them I owe the stimulation of my interest in the study of shock and other disturbances of the body fluids in surgical patients, and the encouragement and opportunities for investigation on which that interest was nourished and grew The late K. W Lane first aroused a biochemical interest which has been maintained and its practical application made possible by Dr C. P Stewart, to whom and to his colleagues I am indebted for much assistance during the last 18 years. To the members of the staffs of hospitals in Edinburgh and Aberdeen,

and especially to Mr. T. McW. Millar and Mr. W. A. D. Adamson, I am greatly indebted for allowing me to study and to treat patients under their care and for giving me the advantages of their watchful interest and experienced advice in the interpretation of the confusing problems I encountered. From the many resulting discussions at the bedside and elsewhere are derived in no small part the opinions expressed in this book.

I am indebted to Messrs. Butterworth & Co. Ltd. for allowing me to incorporate material from a chapter in *Surgical Progress* 1953 for the sections on shock, anuria, loss of intestinal secretions and plasma substitutes and for allowing me to reproduce part of Table II, Table V and, in a modified form, Table IV. Tables XII-XV are modified from similar diagrams by Gilman and Brazeau by kind permission of Dr. A. Gilman.

Messrs. E. & S. Livingstone Ltd. have produced this book with their usual high skill and craftsmanship, and I am very grateful to them for all their help

October, 1955 A. W. W.

CONTENTS

CHAPTER 1

THE CONTENT AND DISTRIBUTION OF WATER, SODIUM AND POTASSIUM IN THE BODY

It is not usually difficult to collect and measure the total volume and even the concentrations of some of the constituents of fluid which is lost by vomiting, discharge from a fistula or in the stools. To make the fullest use of these measurements there must be some knowledge of the composition of an individual body at the outset of an illness as well as at particular stages during treatment, with such information the effects of the fluid losses in producing the clinical disturbance may be judged, as well as the margin of tolerance which remains and the rate, type and quantity of replacements Unfortunately no two human bodies are exactly alike and the range of variation about the mean for age, sex, weight or height is large. There is no close relationship between weight, height, fatness, muscle mass or bone weight, and therefore estimates of the body content of water, sodium, potassium or any other constituent which are not based on direct measurements in the individual but are calculated from so-called standard tables must be subject to large errors. In spite of this, such estimates are often of great value in judging the effects of disease and in designing suitable treatment.

RELATIONSHIP BETWEEN BODY FAT AND WATER

The quantity of water in the human body has usually been assumed to be a fixed proportion, about 70 per cent., of the total body weight the observed body weight has also been used for the calculation of plasma and extracellular fluid volume in attempts to control fluid replacement therapy with greater accuracy Recently it has become evident that when such estimates ignore the presence of storage fat in the body, they may be very inaccurate and misleading Hardy and Drabkin (1950) found that blood volume might vary from 70 ml. per kg body weight in a very obese subject to 105 ml per kg in a very thin one, yet Gibson and Evans (1937) had shown that in subjects of about average nutrition blood volume was closely related to height

More recently Allen *et al.* (1956) have analysed a large number of their own and published determinations of blood volume, and have concluded that the fat content of the body is the most important variable factor and that blood volume is in general related most closely to a combination of body weight and the cube of the height rather than to height or surface area, to a cubic rather than a square function.

The acute changes in volume and distribution of water and electrolyte which are associated with surgical operations and inflammation of all kinds do not involve body fat, which in this connection may be considered as inert tissue On the other hand, the catabolism of storage fat as a source of energy during many kinds of disease and after injury is one factor causing the marked loss in weight, such weight loss is another source of error in the calculation of fluid volumes from whole body weight

Fat floats on water, and fat people are more buoyant than lean ones. When the fat content of a body increases, the density of that body in water diminishes and its specific gravity becomes less. By weighing a body in air and when submerged in water its specific gravity can be directly measured, and from this figure the fat content of the body can be calculated. Behnke (1942) found that fat content had an important bearing on the functional efficiency of the body and that men whose fat content was excessive did not well withstand high-altitude flying or deep diving. It is well known that, in general, unduly fat people are not good subjects for surgical procedures, and this has been commonly ascribed to their poor mechanical efficiency. obese patients are more difficult to move in bed, cough with more difficulty and have to exert themselves more because of their larger bulk, some are so fat that they cannot sit up without help and a few become breathless and cyanosed if laid flat in bed.

From an analysis of body composition in a large number of men, Behnke postulated a basic body structure of relatively constant composition which he called the "lean tissue mass". This consists of 70 per cent water, 20 per cent. solids and an irreducible minimum of 10 per cent. of structural fat. This type of composition is not peculiar to the human species It was found (Pace and Rathbun, 1945, Rathbun and Pace, 1945) that in six species of small animals, including the guinea-pig and monkey, although the fat content varied widely the lean tissue mass was

fairly constant, and when excess fat was excluded the lean tissue mass contained about 73 per cent. water

When storage fat is superimposed on this basic structure, the body weight increases and although the weight and composition of the lean tissue mass do not alter, the percentage of water in the whole body decreases. The fat content of the body may vary from 10 per cent to nearly 50 per cent of the total body weight, and in excessively obese subjects the body water may be less than 40 per cent. of the total body weight.

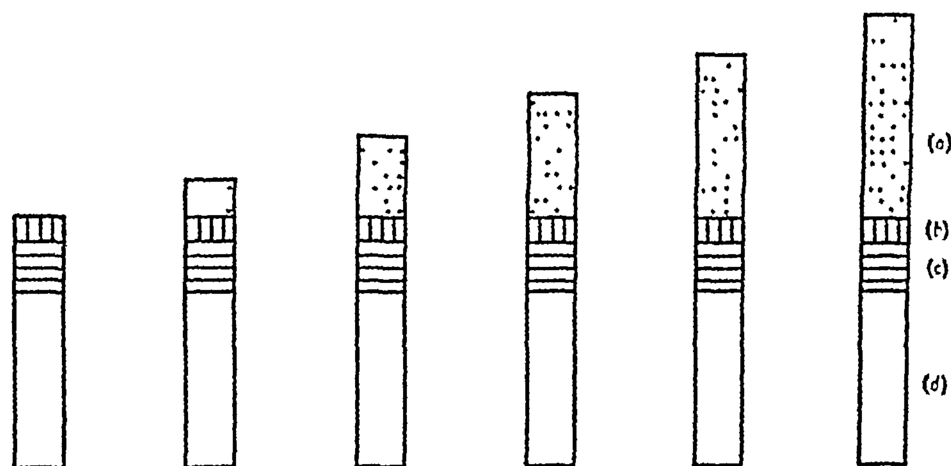
TABLE I

The Effect of Increasing the Fat Content of the Body

	Total Body Weight (kg)	Fat			Solids (kg)	Water	
		Basic (kg)	Storage or Excess			% Body Weight	litres
			kg	% Body Weight			
Basic Structure	60	6	—	—	12	70·0	42
Average Man	70	6	10	14·2	12	60·0	42
Fat Man	80	6	20	25·0	12	54·0	42
	90	6	30	33·0	12	44·5	42
Very fat Man	100	6	40	40·0	12	42·0	42
	110	6	50	45·5	12	38·0	42

The effect of increasing the body content of fat is shown in Fig 1 and Table I For the sake of clarity, the basic quantities of water, solids and structural fat have been shown unchanged throughout, although small changes do occur The basic structure is that of an unusually thin person without any storage fat. The normal individual is represented by the second block diagram (Fig 1) and he contains water equivalent to 60 per cent. of his body weight and storage fat equal to 14 2 per cent. of body weight, this is the composition of an average healthy male subject. In

the remaining four block diagrams, as the proportion of fat increases the proportion of body water falls, and this relationship is also shown in Fig. 2, in which the declining percentage of body water and the increasing percentage of fat are plotted against body weight. The fat content of healthy adults normally increases with age (Brožek and Keys, 1952) from 10 per cent. at the age of 20



	BASIC STRUCTURE	NORMAL ADULT MALE	INCREASING DEGREES OF FATNESS			
TOTAL BODY WEIGHT						
Stones	9st 6lb	11st	12st 8lb	13st 8lb	15st 10lb	17st 4lb
Lb	132	154	176	190	220	242
Kg	60	70	80	90	100	110
STORAGE FAT						
Kg	0	10	20	30	40	50
% Body Weight	0	14	25	33	40	45
TOTAL BODY WATER						
Litres	42	42	42	42	42	42
% Body Weight	70	60	54	45	42	38

Key—(a) Excess or "Storage" fat, (b) Essential or structural fat; (c) Lean tissue solids, (d) Water

Fig. 1.—The effect of increasing the fat content of the body.

years to 25 per cent at the age of 55 years, and females are usually fatter than males

Because of the practical difficulties associated with direct measurement in surgical patients of total body water and its subdivisions such as extracellular fluid and plasma volumes, it is often useful to be able to calculate the total body water of a patient from body weight. The inverse ratio between fat content and body

water renders such calculations from total body weight misleading unless allowance is made for excess of storage fat. McCance and Widdowson (1951) suggested that calculations of this kind should be based not on the actual measured weight of the patient but on the "ideal weight" of the individual, and this is probably the best method to employ in clinical practice. "Ideal weight" is a function of sex, height and age, and can be obtained from standard tables such as those of the Metropolitan Life Insurance Company

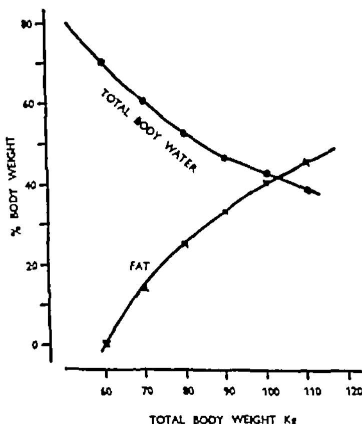


FIG. 2.—Relationship between rising fat content and declining water content.

Allen *et al.* (1956) have collected data from which they have derived formulas with which both the blood volume and the fat content of any individual can be calculated They believe that their method of calculation is accurate in spite of variations in race, age, sex, obesity, malnutrition or the periodic effect of sex hormones They have found that in infants and children before puberty there is no variation between sexes, and although in non pregnant women the blood volume is 600 ml. less than in

males of the same height and weight, in pregnancy it is a litre more, there are also variations according to the phase of the menstrual cycle In both sexes blood volume declines with age. By means of these formulas the actual fat content of an individual can be calculated from his observed weight and can be compared with the previous state in health if the earlier healthy weight is known. In addition changes in total red cell volume and plasma volume can be estimated from actual measurements of packed cell volume and the calculated total blood volume.

For blood volume their formulas are.

Men and boys:	$B.V. = 0{\cdot}417\,H^3 + 0{\cdot}045\,T.B.M. - 0{\cdot}03\,L$
Adult women:	$B.V. = 0{\cdot}414\,H^3 + 0{\cdot}0328\,T.B.M. - 0{\cdot}03\,L.$

For fat content the formulas are

Males:	$A = 0{\cdot}685\,T.B.M. - 5{\cdot}86\,H^3 + 0{\cdot}42$ kg.
Females:	$A = 0{\cdot}737\,T.B.M. - 5{\cdot}15\,H^3 + 0{\cdot}37$ kg.

(B.V. = blood volume in litres. H = height in metres.
T.B.M. = body weight in kg. A = fat content in kg.)

BODY CONTENT OF WATER

The total body water has been measured directly in normal human subjects by the dilution technique with various tracer substances The main essential of a suitable substance for this purpose is that it shall diffuse rapidly throughout the water of the body. "Heavy water" (deuterium oxide) which occurs naturally and contains the heavy isotope of hydrogen (deuterium) is similar chemically and biologically to ordinary water and is an ideal substance for the purpose. It diffuses rapidly through cell membranes and reaches equilibrium after a single injection in two to three hours in adult men, it is non-toxic and about half the dose is excreted in nine days; the plasma concentration remains constant for 19 hours after equilibrium has been reached (Elkinton *et al.*, 1944). Antipyrine also has been used but recently 4-aminoantipyrine has been found to give more accurate results.

Comparable results have been obtained with deuterium oxide (Schloerb *et al*, 1950) and with tritium (Prentice *et al*, 1952) of 60 to 62 per cent. of body weight in normal men and 52 per cent. in women These values may be rather high, and those obtained

with antipyrine (Soberman *et al.*, 1949) of 56 per cent. of body weight in men and 48 per cent in women are probably too low, although they agree well with estimates made from specific gravity measurements of the whole body Edelman *et al* (1952) found that the water content is highest in the newborn infant, 77 per cent. of body weight, falls rapidly during the first 6 months of life to below 65 per cent and more slowly during the next 10 years to an average of 59 per cent The ratio of total body water to surface area increases progressively up to about the age of 12 years, but the absolute volume of body water is highest in males aged 16 to 40 years. From puberty onwards the water content of males is about 7 per cent higher than that of females, but falls slightly in both sexes after the age of 50 years They concluded that the average water content of healthy adults is 61 per cent of body weight in males and 54 per cent. in females, the difference being due to the higher fat content of females after puberty

DISTRIBUTION OF BODY WATER

It has been customary to consider that in the living organism water does not exist free and unattached, but that as water of hydration it forms part of the complex ionic equilibria which make up cell substance and the body fluids, much of the water probably exists in apparently loose combination as a gel It is uncertain how valid a conception this is, but it is undoubtedly helpful to the understanding of the probable distribution and control of water in the human body The total quantity of water in the body is related to the total quantity of cations, particularly of sodium and potassium which in their turn govern the total content of anions and their associated water

TOTAL CONTENT OF SODIUM AND POTASSIUM

Sodium and potassium appear to be the most important of the cations in the control of water, for although they account for only a small proportion of the total mineral content of the body they are its most active components (Table II) The total quantities of sodium and potassium in the body can be estimated directly only by the chemical analysis of the whole body Apart from the

difficulty of obtaining bodies for this purpose, the disease which kills the patient may cause much alteration in the composition of the body. Widdowson *et al.* (1951) analysed four bodies and found wide differences in composition related to age and pre-existing disease. The dilution principle employing the radio-active isotopes of sodium and potassium is widely employed in research but is of limited value for routine clinical purposes

TABLE II

Total Cation Content of the Body

	g	mEq.
Magnesium (Mg) . .	20	410
Potassium (K) . .	135	3,400
Sodium (Na) . .	90	3,900
Calcium (Ca) .	1,120	14,000

Normal Composition of Plasma

Cations (mEq /litre)		*Anions (mEq /litre)*	
Na^+	140	Cl^-	103
K^+	5	HCO_3^-	25
Ca^{++}	5	HPO_4^{--}	2
Mg^{++}	2	SO_4^{--}	1
		Organic acids	5
		Protein	16
	152		152

This method measures the quantities of sodium and potassium in the body with which the injected radioactive material equilibrates or exchanges, or the "exchangeable sodium (Na^e) or potassium (K^e)". Suitable doses of ^{24}Na and ^{42}K are injected intravenously and urine is collected for 22 hours and at the end of 23 and 24 hours. From the specific activity of the last two specimens the dilution of the injected radioactive materials can be calculated, corrections being applied for decay and the measured quantities excreted in the urine during the 22 hours of equilibration Both sodium and potassium have a quick primary phase of equilibration lasting about 30 minutes which may be much modified by variations in the activity and blood flow of organs such as the kidneys and liver, and a slow phase which is complete after 18 to 20 hours The cumulative error of the method may amount

to ±5 per cent. and significance cannot be given to changes in total body content of less than 250 mEq

Moore *et al.* (1954) combined their own large volume of data with that of Forbes and Perley (1951) and concluded that in healthy male adults the total exchangeable sodium (Na^e) amounts to 42·1 mEq per kg body weight and the total exchangeable potassium (K^e) to 46·3 mEq per kg body weight For a typical 70-kg male adult this implies exchangeable contents of 2947 mEq

TABLE III

Total Quantities of Sodium and Potassium in the Body

Exchangeable K = 46·3 mEq per kg body weight
= 3241 mEq in man weighing 70 kg
Exchangeable K = 95% total content of K

$$\text{Total content of K} = \frac{3241 \times 100}{95} \text{ in man weighing 70 kg}$$
$$= 3411 \text{ mEq}$$

Exchangeable Na = 42·1 mEq per kg body weight
= 2947 mEq in man weighing 70 kg

Of the Na in bone, 55% is not exchangeable and this quantity is equivalent to about 25% of total body Na

Exchangeable Na = about 75% total body Na.

$$\textit{Total content of Na} = \frac{\text{Exchangeable Na} \times 100}{75}$$
$$= \frac{2947 \times 100}{75}$$
$$= 3929 \text{ mEq}$$

sodium and 3241 mEq potassium (Table III) They had previously estimated that 95 per cent. of the total potassium in the body was exchangeable with isotopic potassium so that the total body content of potassium is probably in the region of 3410 mEq (133·0 g) for the theoretically typical male adult weighing 70 kg They have also estimated that in the case of sodium about a quarter of the total body content situated in the bones is not exchangeable, and from this estimate and their figure for exchangeable sodium it can be calculated that the total body content of sodium is about 3920 mEq (90·0 g) The manner in which the total exchangeable sodium and potassium are theoretically distributed in the body depends on the concentrations ascribed to sodium and potassium in the intracellular fluid. This in turn depends on the methods which are used to measure the volumes

of total body water and extracellular fluid from which the intracellular fluid volume is deduced. For example, Corsa *et al.* (1950) concluded that the intracellular concentration of potassium was 125 mEq. per litre, a value which was also obtained by Ikkos *et al.* (1954) when they measured total body water with

TABLE IV

Partition of Body Fluids, Sodium and Potassium [1]

70-kg. man (11 st. or 154 lb.)

Total body water=60 per cent. body weight=42 litres

	Extracellular Fluid		*Intracellular Fluid*	
	Plasma	*Interstitial Fluid*	*Soft Tissues*	*Bone*
% Total body water .	7	21	60	10
Volume (litres)	3	9	26	4
Sodium .	43·4% of total 38·6 g. or 1680 mEq Av. 140 mEq./litre		9% of total 8 g. or 390 mEq Av. 15 mEq./litre	47·4% of total 42·3 g. or 1840 mEq. Av. 460 mEq./litre
Potassium .	2% of total 2·34 g. or 60 mEq Av. 5 mEq./litre		98% of total 130 g. or 3360 mEq. Av. 112 mEq./litre	

[1] This scheme of distribution is arbitrary and is based on standard assumed volumes for plasma, interstitial fluid and intracellular fluid. The distribution of sodium has been calculated from these volumes and from the concentrations shown in the table for extracellular fluid and soft tissues, non-exchangeable bone sodium being taken as 25 per cent. of the total body sodium and 55 per cent. of bone sodium (Table III).

antipyrine and extracellular fluid with insulin or thiosulphate; when Ikkos *et al.* used heavy water to measure total body water, their value for extracellular potassium concentration was 112 mEq. per litre, as was found also by Deane and Smith (1952).

About 98 per cent. of the total potassium is in the intracellular fluid, mostly in skeletal muscle, at a concentration of about 112 mEq. per litre, and only about 2 per cent. is in the extracellular fluid at a concentration of about 5·0 mEq. per litre (19·5 mg./100

ml.) It was formerly assumed that there was comparatively little sodium in the intracellular fluid, nearly all of it being extracellular It is now possible to assign to sodium a different distribution which is shown in detail in Table IV In the 12 litres of extra cellular fluid there are 1680 mEq of sodium at a concentration of approximately 140 mEq per litre (322 mg/100 ml) From histochemical analyses, Hastings (1941) estimated that the intracellular sodium concentration was 16 9 mEq per litre, but recently Deane and Smith (1952) using isotopic sodium have put the figure as high as 37 mEq per litre. Edelman *et al* (1954) estimated that bone sodium was equal to about 23 mEq per kg body weight or a total of 1610 mEq in a 70-kg male adult. If Deane and Smith's figure for total intracellular sodium is corrected for bone sodium, a figure of 15 mEq for the soft tissue is obtained, which agrees well with Hastings estimate On this basis the body sodium can be distributed as is shown in Table IV Although there is almost as much sodium in bone as in the rest of the body, 80 per cent. of the sodium which is not in the bones is situated in the extracellular fluid.

SUBDIVISIONS OF BODY WATER

Intracellular Water—The largest subdivision of the water of the body is that of intracellular fluid (70 per cent. of total body water) (Table V) This has a complex distribution in many small

TABLE V

Partition of Body Water

	Total Body Water %	*Ideal Body Weight* %	*Volume in 70-kg Adult (litres)*
Total body water	—	60·0	42
Intracellular fluid	70	42·0	30
Extracellular fluid	28	16·8	12
Interstitial fluid	21	12·6	9
Plasma volume	7	4·2	3

compartments separated from each other by two cell membranes and a layer of interstitial fluid The intracellular water forms part

of the protoplasm of the cells and is associated with potassium, the most important intracellular cation, and with phosphate, the main intracellular anion. The sodium content of intracellular fluid is low except in the skeleton, but nearly half of the sodium of bone is now recognised to be "exchangeable" with sodium elsewhere in the body. All exchanges of intracellular fluid take place through the extracellular fluid and depend on the maintenance of an adequate volume of extracellular fluid as an environment for the cells. The volume of the intracellular fluid can be measured only indirectly, as the difference between the volume of total body water and extracellular fluid. Any attempt to follow closely the day-to-day changes in intracellular fluid volume and composition is therefore limited by the difficulties and errors associated with repeated measurement of total body water and extracellular fluid volumes.

Extracellular Water.—The extracellular water of the body amounts to about 28 per cent. of the total body water and forms the environment of the cells. It is subdivided into intravascular and interstitial portions. The intravascular fluid (7 per cent. of body water or 4·2 per cent. of "ideal" body weight) is situated within the blood vessels, whereas the extravascular extracellular fluid, or interstitial fluid, lies outside the blood vessels and amongst the cells of the tissues of which it forms the immediate environment. The most important cation in extracellular water is sodium, and the content of potassium is very small; chloride and bicarbonate are the predominant anions of this fluid. Apart from the large protein content of intravascular fluid there are only small differences in chemical composition between intravascular and interstitial fluid. The volume of the extracellular fluid can be measured by the dilution of a substance which passes freely through the walls of the blood capillaries but does not enter freely into the cells of the body. Many substances have been used, but most (like thiocyanate) enter the cells to some extent or (like inulin) reach equilibrium in plasma and interstitial fluid rather slowly, so that some of the injected material is excreted before equilibrium is achieved. Others, like sucrose, may be partially metabolised before they reach equilibrium; with thiosulphate, inulin and mannitol the values obtained are low, whereas with thiocyanate or radioactive chlorine, bromine or sodium the values are high. Measurement of extracellular fluid volume is thus easy

but inaccurate. Plasma volume may be measured by the dilution principle, for example by injecting albumin labelled with radioactive iodine (^{131}I) or by injecting the blue dye T 1824 ("Evans blue") which is adsorbed on to plasma albumin, the latter method is probably the most convenient and desirable for clinical use

The intravascular fluid, although small in total volume, circulates rapidly within the blood vessels and exchanges across the capillary walls with the interstitial fluid The latter flows amongst the cells and exchanges occur between it and the intracellular fluid. The normal volume relationship of about 1 3 between plasma and interstitial fluid is maintained in spite of very large daily exchanges of fluid It has been estimated that there is a daily transfer of 1100 litres of fluid between plasma and interstitial fluid, and each day up to 8 litres of fluid are secreted into and reabsorbed from the intestine. The great permeability of capillary and cell walls to water is illustrated by the rapid equilibration of heavy water in the living body, a 'steady state' being reached in both cells and extracellular fluid within about two hours of injection

Water and other constituents of cells are constantly in movement and exchanging between cells and their environment Such arbitrary subdivisions of body water as have just been described are helpful in the visualisation and interpretation of changes in body composition only if it is remembered that they are descriptive of momentary endpoints in a continuously changing process of equilibration.

CELLULAR MEMBRANE PERMEABILITY AND FLUID EXCHANGES

It is now evident that the cell membrane does not completely segregate sodium and potassium as was previously thought to be the case. Such a conception cannot explain the presence of potassium inside living cells and must deny the possibility of exchange of these ions across the cell wall The cell membrane is permeable to both sodium and potassium, and in some cells, such as those of the nervous system, specialised function appears to depend largely on the electrical effects of variations of this kind of chemical transfer The different rates at which sodium and potassium are thought to cross cell boundaries probably depend primarily on certain inherent properties of the ions, but the

difference is not completely understood. Potassium is known to penetrate a cell boundary more rapidly than sodium, the diameter of the potassium ion is only 3.0 Å while that of sodium is 4.5 Å and this property may be enhanced by the negative electrical charge on the cell membrane and by transient local changes in *p*H (Baldwin, 1949). Although all ions carry a positive or negative electrical charge and equality exists between the total sum of the cations and anions and their respective electrical charges, local potential differences across cell walls and in nerves not only exist but are perhaps the basis of much selective function. It is believed that substances may cross a membrane in one of two ways: by permeation which is passive, or by "active transport" which requires the expenditure of energy. A state of equilibrium implies that the flow in both directions is equal rather than that flow has ceased. Passive permeation probably occurs in part at least through so-called "pores" which some believe to be actual openings in the membrane. If, however, the wall is made of lipoprotein it has both polar and non-polar activity and will allow crystalloids and lipoids to pass through; substances such as oxygen, carbon dioxide, ammonia and urea are both lipoid and polar and can pass freely through membranes in both directions without the expenditure of energy. Any membrane may be a mosaic of areas of different degrees of porosity and permeability and there may be some with specific permeabilities for particular substances. Pappenheimer (1952) suggested that 70 to 80 per cent. of the capillary membrane was lipoid in character and so oxygen and carbon dioxide can readily cross it, a fortunate provision for respiratory and tissue gaseous exchange.

The nature of the membrane varies widely. There may be only a single layer of molecules interfering with otherwise free diffusion, or there may be multiple molecular layers with specific activities in controlling or promoting the movement of substances into or out of cells. There are three possible mechanisms of "active transport" across a membrane. A complex molecule, which is soluble in the cell membrane, may be formed with the substance to be transported. Another possibility is that a complex is formed with a carrier molecule which is itself part of the membrane, involving the later breakdown of the primary complex and the formation of another complex in the reverse direction. The third possibility is that the movement of a charged particle leaves

unoccupied an oppositely charged particle which may then be balanced by the movement of another particle of suitable charge

The rate of transfer through a membrane depends firstly on the number of molecules bombarding its surface, that is on the concentration of the solution, and also on the ratio of the concentrations of a substance on the two sides of the membrane. It also depends on the number, type and shape of the so-called "pores" in the membrane and the relation between the shape and size of the molecules to be transported and the pores of the membrane, and on the solubilities of the solute and solvent in the cells of the membrane.

Sodium is the most important cation in the extracellular fluid, the total volume of which is related closely to the total body content of sodium Sodium passes freely across the capillary wall and cannot play any decisive part in the allocation of extracellular fluid between plasma and interstitial fluid The control of the passage of fluid across the capillary wall in both directions is believed to depend on two pairs of factors First, the hydrostatic pressure of the plasma within the vessels and the colloid osmotic pressure of the interstitial fluid move fluid from the plasma into the interstitial fluid. Secondly the hydrostatic pressure of the interstitial fluid outside the vessels and the osmotic pressure of the plasma proteins inside the vessels, which have both been increased by the outflow of fluid from the capillaries, move water back into the vessels from the interstitial space. This general hypothesis depends on the supposition that the capillary membrane is permeable to water and sodium, potassium, chloride and bicarbonate but not to plasma albumin and globulin. Although broadly true for the normal peripheral capillaries this hypothesis does not apply in all circumstances. Since the classic work of Lister there have been many observations of the variable behaviour of the capillary circulation.

In some circumstances there may be an outflow of fluid at the arteriolar end of a capillary and inflow at its venous ends, and under other conditions outflow throughout the length of a capillary, the fluid returning into the same or another vessel or through the lymphatic channels (Chambers 1948) The hydrostatic pressure in the portal venous capillaries is so low that fluid exchange would be impossible if these vessels were not unusually permeable to albumin and thus allowed fluid to cross their walls

The increased peripheral capillary permeability to albumin which is a prominent feature of the inflammatory reaction is associated with a very large local increase in the volume of interstitial fluid and in the rate of its formation, and in the volume of lymph leaving the part.

The lymph vessels open out of the so-called interstitial space and offer another channel of drainage from this space. This is particularly useful for the removal of protein from this space, especially during inflammation, but also allows of the easy return to the blood of the small quantities of plasma proteins which are lost from even normal capillaries. When the intravascular colloid osmotic pressure is lowered by reduction of the concentration of plasma protein or when the outflow of fluid containing protein from the capillaries is increased by an elevation of venous pressure, for example in cardiac disease, the lymph flow also increases.

The movement of water between extracellular and intracellular fluids has been supposed to be controlled by osmosis in such a way that the osmotic pressures of the two fluids remain equal on the two sides of any membrane no matter how the composition of the fluids varies. This view depends on the assumption that all cell membranes are freely permeable to water and that osmotic equilibrium is not disturbed by the active transport across cell membranes of water alone, unaccompanied by other materials

It was originally thought that the high concentration of sodium outside and the low concentration of sodium inside cells arose in some unknown fashion during the original development of the cell, and was thereafter maintained throughout its lifetime by the cell wall becoming impermeable to all cations. This view possibly arose from the consideration of results of short-lived experiments in which there was too little time for changes of cation content to occur. Observations on excised muscle and red blood corpuscles have shown that both sodium and potassium may enter and leave cells, according to the nature of the medium, its content of sodium or potassium and its *p*H. Dean (1941) suggested that these active exchanges of cations might be explained by the existence of a "pump" system. When potassium was forced or pumped into cells, there might be a complementary output of sodium, and inward movement of sodium was accompanied by a complementary output of potassium. Maizels (1949) has pointed out that the presence of a large amount of relatively static protein

and organic phosphate within the cells would permit the active uptake of potassium but would oppose the output of sodium The permeability of the cell wall to cations diffusable anions and water would lead to progressive diffusion into the cell until it burst. The chief cation of the environment of the body cells is sodium, and the cells require some means of extruding sodium if they are to keep their cation content steady and if they are to survive. Maizels has shown that this occurs in non nucleated red cells He has also suggested that the active extrusion of sodium does not necessarily imply the active uptake of potassium, and that the passage of potassium into cells is passive and secondary to the extrusion of sodium

The concentration of cation is higher inside the cells than in their surrounding medium, and this intracellular hypertonicity has been explained in various ways. Peters (1944) suggested that it was due to some of the elements existing in an osmotically inactive form. Robinson (1950, 1953) showed that tissue slices remain normal only so long as their oxygen uptake is normal, and when this is depressed by cyanide they swell up because of absorption of water from the medium He suggested that the hypertonic state of the intracellular fluid can be maintained only by the expulsion of water as fast as it enters. This expulsion of water requires the ' active transport" or ' secretion of water out of the cells, a process which involves the expenditure of energy Active trans port is dependent on an adequate supply of oxygen and its utilisation by cellular enzyme systems. When oxygen is lacking or its utilisation is interfered with, the cells swell because water accumulates within them. It has been shown also that when adequate oxygen is made available to such swollen cells they shrink if they have not been anoxic for too long a period of time. Although little is yet known about the active transport of water, it is not surprising that such a process exists for the control of water content by cells of which water is so large a component, and which live in an even more watery medium Such control may increase the stability of the individual cell and give it some independence of its medium even although that medium so largely conditions the behaviour and ultimately determines the survival of the cell.

Ussing (1952) has explained in a similar way the low sodium content of cells in a medium with a high sodium content, the sodium which diffuses into the cell being as rapidly expelled by an

active process of extrusion. The maintenance of a high potassium content by cells in a saline medium was shown by Terner *et al.* (1950) to be dependent on the presence of oxygen, glucose and L-glutamate in the medium; the absence of any one of these caused a loss of potassium from the cells, but restoration of the missing substance to the substrate was followed by restoration of the potassium content of the cells

Even if it is possible for free water to traverse cell boundaries, it seems likely that on the whole there is a close association of water with cation and anion shifts which are normally accompanied by the movement of water.

WATER BALANCE

The maintenance of the water content of the body depends on the preservation of a state of balance between daily intake and output or loss of water, both of which may normally vary within wide limits. For the present purpose the requirements of water intake are best considered in the light of what is known of water loss from the body.

Water Loss.—Water loss may be divided into two parts: first, the extrarenal loss in the form of insensible water loss as vapour in the expired air or through the skin, or as liquid in the faeces and sweat; and secondly, the renal water loss as the urine.

EXTRARENAL WATER LOSS. *Insensible Water Loss.*—This is made up of two components. The first is the water vapour which saturates the expired air and which varies in quantity with the rate and depth of respiration. The second component consists of the water vapour which diffuses through the skin into the surrounding air. This kind of loss depends on the difference in water content of the body and its environment, and its rate varies with body temperature and thus with metabolic rate, with the temperature and humidity of the environment, and with the clothing or bedding covering the body. Insensible water loss by vaporisation plays an important part in the dissipation of the heat generated by metabolism, and hence in the regulation of body temperature, and is essential for survival. It should be regarded as inevitable and as the primary water requirement of the body which continues and must be satisfied so long as the body is alive, regardless of the water requirements for urine formation and

abnormal losses of body fluids. It is distinct from the loss of water by sweating, which depends on the secretion of sweat by the sweat glands. Sweating is an accessory means of promoting heat loss by the evaporation of water when the body temperature tends to rise because of an increase in heat production reduced heat loss due to excessive clothing or elevation of the temperature or humidity of the environment.

The average insensible loss of water through the skin and in the expired air was estimated by DuBois (1936) to be 0 5 g of water per kg body weight per hour in adults (840 g of water per day in a 70-kg man) a similar estimate was made by Gamble (1947) as the result of repeated weighing of normal adults under varying circumstances, and he showed also that this basic rate of loss was increased by clothing and by changes in environmental conditions Newburgh *et al* (1937) found that loss of water vapour from the skin of normal men varied with the air temperature when they were naked, but when they were lightly clothed the loss varied little over a wide range of temperature. They concluded that when a man is comfortable in his environment about one quarter of the total heat produced in the body is dissipated by insensible water loss, even when the calories consumed vary from 2200 to 3600 per day, or when 6 per cent. of body weight has been lost by dehydration. Estimation of insensible water loss from metabolic rate gives a higher figure than the other methods but being based on energy expenditure and thus related directly to heat production approaches the true figure more closely, for example, a subject metabolising 2500 calories per day and dissipating one-quarter of this heat by insensible water loss will evaporate $\frac{2500}{4} \times \frac{1}{0{\cdot}58}$ ml of water per day = 1077 ml. water regardless of his body weight. Unfortunately, in many disease states associated with partial dietary starvation, direct measurement would be necessary to estimate the energy derived from the catabolism of body fat and protein. Body metabolism rises by 7 per cent. for each 1° F rise in body temperature (13 per cent. per 1° C) so that an increase in insensible water loss results from pyrexia.

Man is able to get rid of a constant proportion of his daily heat production by insensible water loss and thereby retains his state of comfort in his environment. When he feels uncomfortably warm or cool, he can modify the disparity between himself and his

environment by altering the rate of heat production or by changing the environmental conditions. The important practical aspect of these observations lies in the comfort associated with the normal rate of heat production and loss; the surgeon who finds the atmosphere of his operating theatre neither too hot and humid nor too cold is unlikely to be inflicting an undesirable environment and excessive rate of water loss on his unconscious and defenceless patient.

Sweat.—The evaporation of sweat provides an additional means of dissipating body heat especially when at low relative humidity the environmental temperature exceeds 84° F. (29° C.) or heat production is very large; when the humidity is higher, sweating begins at lower temperatures. Whether sweating is noticeable depends on how rapidly it evaporates, which in turn is related to the humidity as well as to the temperature of the environment. The volume of sweat varies widely between individuals in the same circumstances, and up to 3 litres may be produced in an hour or 10 litres in a day; such very high rates of sweating are not maintained for long and the rate falls off as exposure to heat is prolonged even if all the lost water is replaced. Ladell (1945) suggested that this was due to fatigue of the sweat glands, which also were less able to regulate the mineral content of the sweat (see p. 40).

Sudden exposure to a high environmental temperature may cause acute disturbances of body fluid equilibrium. This is more likely and important in the small proportion of people who appear to have a poor capacity to make the necessary homeostatic adjustments in the composition and volume of the sweat and urine. Prolonged exposure may reduce the capacity of a patient to deal with the effects of even an uncomplicated surgical operation. This incapacity is now of new importance, for whereas formerly such a patient might have had some time to recover during a sea voyage of three or four weeks from the tropics to Europe he now may return in one day by air. What is perhaps more important is that people may now arrive by air in the tropics without the opportunity of even limited acclimatisation which exists during a sea voyage lasting three or more weeks.

The confusion which has long been associated with the group of disorders which are caused by exposure to heat has partly arisen from the terminology which has been used; recently (1958)

an attempt to resolve this confusion has been made by a committee of the Medical Research Council. By far the most serious and important disturbances are *heat exhaustion*, a disturbance of the body content and distribution of water and electrolytes, and *heat stroke* and *hyperpyrexia*, disturbances due to failure or impairment of the processes involved in body temperature regulation. There is no essential difference between heat stroke and hyperpyrexia except that conventionally heat stroke is the term usually employed for the more severe and fatal forms of this disturbance of temperature regulation.

Heat exhaustion (formerly Type I heat exhaustion) affects the apparently well acclimatised man who has been working daily in the heat. it is characterised by a pale sweating skin and slight elevation of the body temperature and pulse rate, the patient appears 'dehydrated' and to have lost weight, there is haemoconcentration and he passes small quantities of dark concentrated urine containing little sodium or chloride. Muscle cramps may begin before or during treatment (Ladell, 1957). This condition appears to be the result of a chronic depletion of water, sodium and potassium, and affects both intracellular and extracellular fluid. This is primarily due to repeated incomplete replacement of the daily sweat losses incurred during working hours and is indicated by a low urinary volume. Ladell (1947) found that up to two litres of water must be lost from the body before the volume of the saliva decreases or a basal urinary volume is achieved. During acute exposure to heat if water is drunk freely but the salt intake is low the continued small loss of sodium in the urine leads to reduction in extracellular fluid volume although there is no intracellular dehydration. If instead, however, too little water is drunk but supplementary salt is taken, the total body sodium content is well maintained but extracellular fluid volume must be maintained by the withdrawal of water from the cells leading to an intracellular dehydration (Ladell, 1955). In both types of this disturbance the circulatory collapse is the result of reduction in extracellular fluid volume, but in the first this may be associated with a low serum sodium concentration while in the second type serum sodium concentration may be raised. After long exposure to heat, when there is depletion of both intracellular and extracellular fluid, the consumption of a lot of water may cause dilution of the extracellular fluid and muscle cramps but is not likely to cause

circulatory collapse If on the other hand more salt than w
is given, especially as hypertonic saline, after an initial impr
ment there is usually a circulatory collapse. Thus heat exhaus
may be due to drinking too little water in great heat, or to se
exertion combined with the inadequate consumption of w
or salt.

Hyperpyrexia is sudden in onset, affecting a man who w
normally in the morning, may fall mildly ill at midday, colla
suddenly during the afternoon and if not treated promptly is c
by sunset. This is due to failure to dissipate the heat of m
bolism and is closely related to the production of too little sw
as well as to high environmental temperature and humidity. A
collapse the unconscious patient has a bone-dry burning hot s
a rectal temperature of 105° to 107° F. and stertorous breath
Without treatment all these patients will die. The body mus
cooled at once by being wrapped in a wet sheet and laid in
draught from a fan until the rectal temperature falls to 102°
Ice bags should not be used as they induce only local vasoc
striction, and thus by interfering with heat loss may cause
body temperature to rise. Hyperpyrexia may be due to e
exertion in a very hot environment which increases the product
of heat beyond the capacity of the body to lose it, perhaps beca
of unsuitable clothing or poor air movement due to bad vent
tion. It may also be due to inadequate sweating because
prickly heat or other skin disorders or because of an inherent l
limit of tolerance of the individual to climatic extremes. Th
last people are important because ideally they should be detec
and excluded from such risks Reduction in the rate of sweat
is one of the signs of acclimatisation to heat, but there is als
normal falling off in sweat production as the body temperatu
rises Individuals who normally sweat less than their co
panions may have a poorer tolerance to extreme heat and theref
should probably be protected from it

It is believed that prolonged *prickly heat* may upset sweati
function sufficiently to cause *tropical anhydrotic asthenia* (forme
called Type II heat exhaustion). This disturbance of heat regu
tion characteristically comes on gradually towards the end of t
tropical summer after prolonged exposure to heat and is associat
with an inability to sweat properly, moderate pyrexia (up
101° F.), loss of energy and the passage of copious quantities

dilute urine containing little chloride or sodium Such individuals recover slowly over a period of about six weeks in a cool environment on a full diet, and according to Ladell (1957) cannot be more rapidly cured by the administration of saline. The exact cause and the mechanism of this disturbance remain obscure.

Faecal Water Loss —The rate of water loss in the faeces varies with the rate of passage of material through the intestine, especially the colon, and on the degree of dryness of the stools when passed. During fasting the stools are small and contain little water, but on a normal diet it is usual to allow for the loss of up to 200 ml. water per day in the faeces This quantity is approximately equal to the water of oxidation of the food consumed When large quantities of mucus are lost, for example in some forms of malignant disease of the colon and rectum, or when many loose stools are passed as in ulcerative colitis, up to a litre or more of water as well as large quantities of minerals, may be lost from the bowel each day

RENAL WATER LOSS —The renal glomeruli filter about 180 litres of fluid from the 1100 litres of plasma which flow through the kidneys each day About 85 per cent. of this filtrate is absorbed isosmotically in the proximal convoluted tubules. With the exception of rather less than one per cent. of the original volume which forms the urine the remainder of the water is absorbed in the distal tubules The minimum volume of water required by the kidneys for urine formation varies with the total quantity and with the nature of the solutes which are to be excreted, or the "osmotic load", and on the ability of the kidneys to excrete a concentrated urine. The solute or osmotic load varies with the food intake and with the metabolic state of the patient, it is raised by tissue catabolism after injury and in many diseases, and by the production of keto acids when fat metabolism is incomplete. Normal urine is hypertonic in comparison with plasma, and by producing concentrated urine the kidneys play an important part in conserving body water Gamble (1954) has shown how closely the water requirements for urine formation are related to the concentrating capacity of the kidneys the minimum urine volume for a given solute load varying from about 500 ml. at a urine specific gravity of 1032, to 750 ml. at a specific gravity of 1020 and 1300 ml at a specific gravity of 1016 When the intake of water is restricted, the requirements for insensible loss as

vapour through the skin and in the expired air must first be satisfied; if the available water then remaining for urine formation is insufficient to dissolve the solute load, either additional water must be obtained from the body fluids or some of the solute load must be retained in the body. When water is consumed in excess of the requirements for insensible loss and the minimum urine volume, the excess is excreted by the kidneys as additional urine water. A healthy adult with normal kidneys can excrete the daily solute load in 500 to 800 ml. of urine.

The Total Minimum Daily Expenditure of Water.—In a temperate climate for an adult weighing 70 kg. insensible water loss amounts to about 1000 ml., 200 ml. or more may be lost in the faeces and 500 ml. as urine, in all about 1700 ml. In the past too little attention has been paid to the effects on the water turnover of hospital patients, especially after operation, of the large variations in environmental humidity which are inevitable in the continental type of climate. On the other hand too much emphasis has been laid on forcing up the volume of urine by large intravenous infusions to an arbitrary level often much above the minimum requirements. Ladell (1947) has shown that in a temperate climate a resting adult eating an ordinary diet needs to consume only 800 to 900 ml. water per day to remain in water balance.

Water Intake.—On an ordinary diet about 12 g. water are produced from each 100 calories metabolised, equal to a total of 200 g. or more water per day; and the water content of the solid food which varies from 60 to 95 per cent. provides about 300 g. or more in addition. The daily consumption of water by drinking varies widely; some normal people drink as little as a pint (560 ml.) per day, but the average consumption by patients in hospital is about 800 to 1000 ml. per day. In certain occupations which involve heavy water losses by sweating, a gallon or more (4 litres) may be regularly consumed daily. These wide individual variations in water intake and turnover deserve greater recognition and respect when the daily water requirement of the individual surgical patient is being considered. It may be as great a hardship and more harmful for some patients, especially if they are elderly, to drink 5 or 6 pints each day as for others to do without water entirely.

Regulation of Water Content of the Body.—Of the organs

concerned with water exchange, the skin, pulmonary alveoli and air passages are rather passive agents of exchange and only the kidneys have any regulatory effect on water expenditure. The insensible loss of water is dependent on environmental temperature and humidity and on the rate of production of heat or energy consumption of the body The water content of the body is the important factor which initiates change of rate in turnover in the kidneys The absorption of water by the distal renal tubules is controlled by the antidiuretic hormone secreted by the posterior lobe of the pituitary gland under the influence of nervous impulses originating in the supra-optic nucleus, this centre responds to impulses received from osmoreceptors sensitive to changes in the water content of the blood (Verney, 1947, 1954) The antidiuretic hormone mechanism responds to changes in blood composition which are the result of excessive loss or ingestion of water and produces either oliguria (antidiuresis) or increased water output by the kidneys. The osmoreceptors appear to be particularly sensitive to acute changes in the composition of the blood and do not invariably respond so sensitively to chronic or gradual alteration of a degree which if produced acutely would invoke a sharp response. Control of water output by antidiuretic hormone is generally independent of the output of cations such as sodium and potassium and the rate of excretion of these ions may remain steady in spite of a large diuresis induced by the copious drinking of water Following the ingestion of a large quantity of water there is a lag period before diuresis begins while the normal circulating antidiuretic hormone is destroyed, the diuresis can be inhibited by injection of antidiuretic hormone That this control of the volume of the urine is by an antidiuretic hormone emphasises the importance of close limitation of the loss of water by a body of which 70 per cent. is water and which must exist in a drier environment.

Thirst.—The sensation of thirst is not well understood Cannon (1918) believed that thirst had a local origin in a dry mouth. He supposed that the salivary glands which are normally responsible for keeping the mucous membrane moist, suffered from the general lack of water in the body and did not secrete enough saliva to prevent the local discomfort and unpleasantness which constitute the feeling of thirst. Claude Bernard (1856) showed by experiments, with a horse with an oesophageal fistula and a dog with a

gastric fistula, that when these animals were thirsty they drank almost continuously, pausing only for short periods of rest, and he concluded that thirst was not a local sensation but a response to some general demand to raise the water content of the body to a normal quantity His results have been confirmed by Adolph (1947), who found that in thirsty men, and in dogs with oesophageal fistulas, the water deficits were closely related to the quantity of water consumed in slaking thirst or to the urge to drink It seems evident that water is roughly measured in the pharynx as it is drunk. The urge to drink to satisfy a lack of water can be abolished temporarily by sham drinking, by contact of water in the throat, or alternatively and more lastingly by placing water in the stomach through a tube. The intravenous injection of a hypertonic solution of sodium chloride (Leschke, 1918) or sodium bicarbonate (Arden, 1934) causes intense thirst, but after the injection of the same quantity of an equally hypertonic solution of potassium chloride thirst is not experienced. Gilman (1937) found that the intake of water was much larger when the osmotic pressure of the plasma was increased by the injection of a hypertonic solution of sodium chloride than when urea was used. Wolf (1950) raised the plasma osmotic pressure gradually by injecting hypertonic saline and found that thirst began when the osmotic pressure had risen by 1 to 2 per cent., a figure which resembles Verney's estimate for the threshold of release of antidiuretic hormone in the dog. Recently Andersson and McCann (1955) have produced evidence for the existence of a "drinking centre" in the hypothalamus.

Restoration of the water content of the body after depletion depends on the type of water loss which has occurred When water has been lost in association with sodium in extracellular fluid depletion, sodium and water must be replaced in order to maintain tonicity as the volume of extracellular fluid is restored; if sufficient sodium is not introduced, the excess water will be excreted One of the remarkable features of extracellular fluid depletion is the absence of thirst, until it is remembered that thirst, being a stimulus to drink water, would lead to the dilution of the remaining extracellular fluid; it is interesting too that McCance (1936) found that sodium-depleted normal subjects lost all sense of taste and smell, but that this returned soon after the consumption of 15 g. of sodium chloride.

Neither thirst nor antidiuretic activity is aroused by changes in the volume of body fluids provided there is no accompanying change in the concentration of sodium or in total osmolarity A loss of water alone stimulates both thirst and the output of antidiuretic hormone and this is a more effective process than the reponse to an increased body water content, the absence of thirst and a diuresis, an excess of water is fortunately uncommon except following the too lavish intravenous infusion of glucose solution

Intense thirst is experienced by severely injured patients suffering from shock and usually subsides as blood volume is restored by transfusion, this kind of thirst seems to be closely related to the acute reduction in blood volume consequent on blood or plasma loss, and may well be due to the transfer of interstitial and intracellular fluid as part of a compensatory reaction to the acute lowering of blood volume. Severe thirst is also common after major surgical operations even when there has not been a large loss of blood beginning about 6 to 12 hours after operation, it lasts for 48 hours or more, and may persist for up to 6 or 7 days in patients who receive prolonged intravenous infusions.

During the first 24 or 48 hours after operation, thirst can be relieved only for short periods of time, 15 to 20 minutes, by the consumption of water, tea or other fluids and is not relieved by the intravenous infusion of isotonic saline or glucose solution. The period of most intense thirst after operation corresponds in time to the rapid loss of potassium from the cells and to a marked loss of weight. It seems possible that during this period thirst is due chiefly to intracellular dehydration and is a normal effect of injury, transient relief follows wetting of the mouth and pharynx even when the fluid is not swallowed and practically none of it is absorbed. The best relief is obtained by washing out the mouth with ice-cold water, and in practice this is more effective than drinking When after operation the intake of water is stopped for 48 hours, the intense thirst which is experienced from about 12 to 30 hours after operation often diminishes or disappears entirely before any water is drunk (Wilkinson, 1956 b) If large quantities of fluid are drunk, the alimentary tract and especially the stomach appear to be incapable of absorbing them and they are usually vomited. When following operations on the alimentary tract the patient is allowed to drink unlimited quantities of fluid, but distension of the stomach is prevented by aspiration, thirst often

increases. As the quantity of fluid drunk increases, there is an even greater increase in the volume of fluid aspirated, and very large quantities of sodium and chloride, as well as of water, may be lost in the aspirations. Presumably the increasing thirst is due to an increased transfer of water from the cells, leading to "intra-cellular dehydration".

CHAPTER II

SODIUM

NORMAL CONTENT AND DISTRIBUTION

In a normal subject nearly 44 per cent. of the total body sodium is in the extracellular fluid and only 9 per cent. is in intracellular fluid, the remaining 47 per cent. being in bone. About 45 per cent. of the sodium in bone is exchangeable and may take an active part in the continuous rapid interchange of sodium in the body, thus in all about 74 per cent. (66 g.) out of the total of about 90 g. in the body is freely available for so-called metabolic purposes and the compensation of abnormal loss from the body (Table VI).

Table VI

Distribution of Sodium in the Body

Total content 90 g. = 3912 mEq./70 kg. (11 stones)

	% of Total	*g.*	*mEq.*	*Exchangeable*	*Available*
Extracellular fluid	44	39·6	1721	all	74% total 66 g. 2900 mEq.
Intracellular fluid	9	8·1	352	all	
Bone	47	42·3	1839	45%—19·0 g. 827 mEq.	

The quantities of sodium and chloride excreted in the urine vary with the intake and with losses by vomiting, diarrhoea or by excessive sweating due to climatic or occupational factors.

SODIUM EXCHANGES

Sweat.—Sweat is produced chiefly by the cholinergic eccrine glands, which are distributed all over the body. Unlike the insensible water loss through the skin, sweat contains all the

increases. As the quantity of fluid drunk increases, there is an even greater increase in the volume of fluid aspirated, and very large quantities of sodium and chloride, as well as of water, may be lost in the aspirations. Presumably the increasing thirst is due to an increased transfer of water from the cells, leading to "intracellular dehydration".

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SODIUM EXCHANGES

Sweat.—Sweat is produced chiefly by the cholinergic eccrine glands, which are distributed all over the body Unlike the insensible water loss through the skin, sweat contains all the

plasma ions, the most important being sodium and chloride, but is always hypotonic compared with plasma or extracellular fluid. Sweating is caused by a rise in skin and rectal temperature. The rate of sweating is probably not much affected by moderate water deficiency but may stop when dehydration is very severe; it is certainly reduced by the drinking of 0 5 per cent. saline and by the administration of drugs of the atropine group. About 50 per cent. of the sweat is secreted on the trunk, 25 per cent. on the legs and the rest on the arms, head and neck; in hot climates by interfering with heat loss extensive injuries of the skin introduce the additional possible complication of hyperpyrexia. The sweat glands are partly under the influence of adrenal cortical hormones and the composition of sweat varies greatly. When a normal subject is made to work hard for a short time in a hot room he secretes larger volumes of sweat containing much higher concentrations of sodium and chloride than he would do if he had become acclimatised over a period of days to an equally hot climate (Ladell, 1945). The mineral content of sweat varies so widely that average figures cannot be given and unfortunately methods of collection of sweat are not suitable for bedside use. Schwartz and Thaysen (1956), who stimulated sweating with acetyl-β-methyl-choline, found that the sodium concentration varied from 6 to 85 mEq. per litre but was always lower than the plasma concentration, whereas the potassium concentration varied from 5 to 21 mEq. per litre and was always higher than that of the plasma. The concentrations of sodium and chloride in sweat are related also to the intake of these ions and usually decline when their total body contents fall; when the salt intake exceeds that necessary to maintain sodium and chloride balance, the concentrations of sodium and chloride in the sweat rise. It is well known amongst men working in hot humid environments and by dwellers in hot climates that the taste of the sweat on their skin affords a good indication of the salt content of the body; after heavy sweating a salt "frost" may be seen on the cheeks and upper lip and the disappearance of the normal salty taste from the sweat is commonly taken as an indication for the consumption of extra salt. Dill *et al.* (1933) stated that part of the process of acclimatisation to a hot climate was expressed in a reduction in the sodium content of the sweat. This has been confirmed by the work of Conn (1949, 1956) and others on adrenal cortical hormones,

particularly aldosterone, failure to reduce the chloride and sodium content of the sweat during acclimatisation is an indication of adrenal inadequacy or failure. Conn found that in healthy men adrenal influence was so marked that they could be maintained in sodium balance on an intake of only 5 g sodium chloride (85 mEq sodium) per day in spite of copious sweating caused by heavy work in a hot environment. Compared with plasma sweat contains more water than sodium, but the repeated replacement of sweat loss by water alone leads to sodium depletion When the body is depleted of water replacement is stimulated by thirst, but there is no comparable stimulus to the replacement of sodium, and the natural processes of regulation of water and sodium content are different. Sodium content is regulated by conservation, or stabilisation of the body content, by processes which reduce sodium loss by lowering its concentration in secretions such as sweat and urine, probably under the immediate influence of adrenal cortical hormones With increasing use and speed of air travel there is more chance than ever before that unacclimatised passengers may occasionally have to undergo emergency surgical operation in the tropics , if they can be nursed in air-conditioned accommodation severe disturbance of body fluid equilibrium by excessive sweating and mineral loss can be largely avoided At present there is little information on which to base estimates of water and sodium requirements in hot and humid environments during the first week after a major operation or severe injury, and judgment is even more difficult in unacclimatised patients.

Renal Regulation of Sodium.—Except during the first six days or so after injury or during inflammation due to other causes, when sodium intake exceeds the extrarenal losses the excess is excreted in the urine. In adults the glomerular filtration rate varies from 90 to 150 ml. per minute with an average rate of 120 ml per minute, or 70 ml per square metre of body surface area per minute, and is not much affected by the state of hydration as long as the individual continues to eat, only about 0 5 to 2 ml. of urine are formed per minute, which if maintained result in the excretion of 720 to 3000 ml. urine in 24 hours. At a plasma sodium concentration of 140 mEq per litre, 16 8 mEq sodium will be filtered each minute, or if the rate is steady about 24,000 mEq in 24 hours (equivalent to 15 times the total extracellular

sodium), yet only about 100 mEq may be excreted in the urine. At a steady glomerular filtration rate of 120 ml. per minute, 173 litres of filtrate (4 times the total body content of water) would be formed in 24 hours, but less than 1 litre might be excreted as urine Such high rates of filtration are not maintained for long periods, and it is known that there are variations in sodium and potassium excretion between night and day. Even so, very large volumes of glomerular filtrate are formed and a high proportion of this filtrate is reabsorbed in the proximal tubules with little or no modification in its content of sodium, potassium, chloride or bicarbonate (isosmotic reabsorption). Other substances, in particular urea, are not reabsorbed, and so their concentration in the remaining fluid in the renal tubules increases

In the distal tubules the remainder of the glomerular filtrate is further modified by selective reabsorption and secretion by the tubular cells This treatment of the filtrate by the distal tubular cells removes most of the remaining water and sodium and reduces the concentration of sodium in glomerular filtrate, which is the same as that of the plasma, to the varying concentrations of sodium found in the urine in the different states of sodium content of the body. Since the renal tubular cells are themselves probably subject to changes in chemical composition similar to those which occur in other cells of the body in states of deficiency or excess, the tubular cellular function is liable to alteration when the body content of the biologically important ions is disturbed It is for this reason that in advanced stages of deficiency or excess of certain constituents renal tubular function may be upset and can be restored only by specific correction of the disturbance. The small alteration in composition of large volumes of fluid which occurs in the proximal tubules by the isosmotic absorption of water, sodium, potassium, chloride and bicarbonate without urea is an example of a convenient and primitive biological process which avoids secretion with its high energy requirements Similar processes are found in the daily large turnover of secretions, containing up to 100 mEq. sodium in the alimentary tract, and in the peripheral capillary circulation.

Glomerular filtration rate depends on the renal blood flow, and both may fall when blood and especially plasma volume are reduced. The administration or consumption of water, by increasing extracellular fluid volume and so plasma volume, increases

glomerular filtration but not always the sodium content of the filtrate, although the urinary sodium output may rise during water diuresis this is not an invariable consequence, and the control of sodium excretion is not well understood. Desoxycorticosterone acetate causes sodium retention by the tubules regardless of the sodium concentration in plasma The most powerful conservation of sodium is effected by aldosterone, which is about 30 times as effective as desoxycorticosterone acetate.

Sodium in Bone—The importance of the skeleton as a reservoir of the mineral constituents of the body is now recognised. Harrison *et al* (1936) found that half of the sodium in bone was osmotically inactive and soluble in acid but not in water or strong alkali, and they thought that it was part of an apatite complex. The vast surface of the crystals in bone provides an enormous area for the adsorption of sodium, magnesium and potassium in ideal circumstances for a dynamic equilibrium with the extracellular fluid (Robinson, 1951) Bergstrom and Wallace (1954) suggested that sodium might be withdrawn from such a site in bone when the extracellular fluid equilibrium was disturbed by the loss of sodium from the body Much of the exchangeable sodium can be removed from the bones of experimental animals in a few hours after the artificial induction of severe acidosis and the decalcification of bone in chronic renal acidosis or in lactation implies that at least part of the sodium content of human bones is labile, there is, however no evidence that bones can store minerals in excess of their normal content.

It is recognised that in some circumstances the results of careful metabolic balances cannot be reconciled with calculations of the total sodium content of extracellular fluid or of the whole body, Moore (1954) suggested that in such circumstances sodium might have been mobilised from bone. So far only a few direct measurements of changes in sodium content of bone have been made in human patients. Loss of sodium from bone has been shown in animals in acute sodium depletion or with adrenal hypofunction, similar shifts of sodium might occur in patients especially after losses by diarrhoea or sweating in diabetic acidosis, or prolonged restriction of sodium intake or use of mercurial diuretics.

Normal Intake and Output.—It is difficult to decide how much sodium constitutes a normal daily intake because of the

compensatory mechanisms which guard against its depletion. As Ladell (1957) has pointed out, phylogenetically man is a tropical animal and the sweating state is a normal one for the species, but he doubts whether it is natural for the human species to have the high salt intake which is so common in the so-called Western civilisation. He has suggested that the addition of salt to food is a luxury and an addiction and has resulted in habituation to a lower daily plane of aldosterone production, but this attitude perhaps ignores the ancient purpose of preventing the putrefaction of meat in a hot climate by bleeding the animal during slaughtering and thereafter applying salt as a preservative It is clear that a wide range of sodium intake can be tolerated by people with satisfactory renal and adrenal function In a temperate climate the average quantity is probably in the region of 80 to 100 mEq. per day (5 to 6 g. as sodium chloride). About 70 to 90 mEq. (4 5 to 5 5 g as sodium chloride) may be lost in the urine and less than 10 mEq in formed faeces, with varying but usually negligible quantities in sweat (Table VII). Some people habitually consume more and others less than 5 or 6 g. of sodium

TABLE VII

Daily Intake and Output of Sodium

Intake in food	80-100 mEq.
Output in urine	70-90 mEq
Sweat and faeces	about 10 mEq
Secreted into stomach and intestine and reabsorbed	685 mEq.
Filtered by renal glomerulus and reabsorbed up to	24,000 mEq

chloride per day. In temperate conditions an intake of 10 to 15 g. of sodium chloride per day administered as isotonic saline during the first week after operation leads to a large increase in sodium and water content and body weight, and may cause oedema. To limit loss of sodium by sweating, especially in children and young babies, overheating of patients should be avoided during operations; the use of rubber sheeting should be abandoned, because this creates a private environment round the patient of 100 per cent. humidity at body temperature and is equivalent to putting the child in a turkish bath; the temperature of the theatre should not exceed 70° F. and the humidity 65 per cent In an operating theatre in which it is comfortable to work,

emperature and humidity do not usually exceed these limits The so-called "ether" convulsions, which were formerly a not uncommon complication of operations on ill and pyrexial children, were probably due largely to the effects of high temperature and humidity in the operating theatre on a child whose water balance was already seriously upset by disease and a raised body temperature.

In hot climates, if an air-conditioned theatre is not available, operations should be performed in the early morning When sweating is unavoidable, the loss of sodium in sweat should be replaced by the consumption of additional salt according to individual requirements and circumstances, the best indication of an adequate supplement probably being the taste of the sweat. Ladell (1957) has calculated that the average daily intake of sodium chloride by the Nigerian peasant is probably less than 7 g (119 mEq sodium) and he quotes an estimate by Lange that the daily intake of an Indonesian peasant is only 3 g sodium chloride per day (51 mEq sodium) The dangers of treating such people according to the orthodox principle laid down for certain limited and entirely different environmental conditions is obvious. There is no reliable specific information regarding the range of requirements for either water or sodium of surgical patients under tropical or subtropical conditions. There may be wide individual and racial variation in tolerance of heat and humidity, which is complicated by undernutrition and disease, such as chronic dysentery and malaria. There is wide scope for study of these aspects of surgery in tropical countries.

DISTURBANCES OF SODIUM EQUILIBRIUM

Disturbance of sodium equilibrium occurs after injury and in association with all forms of inflammation and is a feature of many diseases. It may result from alteration in the total quantity of sodium in the body or from change in sodium concentration due to alteration in total water content, or from a combination of both these factors. There may also be alterations in the distribution of sodium in the body with or without change in the total body content of sodium. Disturbances of sodium equilibrium can be broadly classified as due to either sodium depletion or sodium

excess. Each of these two main types can be further subdivided into those which are real and are caused by a reduction or an increase in the total body content of sodium, and those which are only apparent, the concentration of sodium in extracellular fluid being altered by variations in water content and distribution in the absence of any change in total body content of sodium. In surgical practice the most common disturbances are due to extra-renal losses of sodium and water following the loss of gastro-intestinal secretions or to the excessive administration of solutions of sodium salts or water; this is in contrast to the situation in patients with severe cardiac and renal disease who are now more commonly subjected to operation than formerly and often suffer from excessive content of water and sodium together with various secondary disturbances. In most clinical circumstances, because both sodium and water are lost, the pure forms of the disturbances of sodium equilibrium are rare. In the absence of severe renal disease, renal conservation of sodium is so efficient that only small quantities of sodium are lost in the urine after surgical operations or severe injury, or during even extensive infective inflammatory disease.

Sodium Depletion

(a) *Real* sodium depletion (so-called "salt depletion") is usually due to the loss of both sodium and water. When the sodium and water are lost in the same proportion as they occur in extracellular fluid, for example in the loss of plasma after burning, the extra-cellular sodium concentration may not change. When a large loss of sodium and water is replaced with water alone or with too much water and too little sodium, the extracellular sodium concentration will fall, for example when a large loss of sweat is replaced by the drinking of water, or when too much glucose solution is used in the replacement of large losses of gastro-intestinal secretions.

(b) *Apparent* sodium depletion or "sodium dilution". In the absence of any appreciable loss of sodium the extracellular sodium concentration is reduced by the administration of water more rapidly than it can be excreted by the kidneys or lost insensibly or by sweating. This is probably most common in elderly patients to whom excessive quantities of glucose solution are administered after operations (water intoxication).

Sodium Excess

(a) *Real*.—The sodium content of the body may be increased by the rapid intravenous administration of solutions of sodium salts. Even a daily intake of sodium which is within the so-called normal limits may increase total sodium content when renal excretion of sodium is delayed after injury or during inflammation, impaired by renal disease or altered by the administration of adrenal cortical hormones or secondary to cardiac disease. Whether the extracellular sodium concentration changes depends on the state of water balance.

(b) *Apparent*.—The extracellular sodium concentration may rise in true dehydration when the total body water content is reduced but the body sodium content is maintained, or when there is a loss of both water and sodium, but the loss of water is the greater.

Dehydration.—This term, which strictly used implies the loss of water alone from the body, is widely and loosely employed to indicate the loss of water and various ions from the body, without any indication being given of the source of the lost water or of the accompanying losses of ions. Kerpel Fronius (1935, 1938) showed that there are two distinct kinds of so-called "dehydration". In one there is a loss of water but not of an equivalent quantity of cation, this loss is accompanied by thirst and the water may be derived from both extracellular and intracellular fluid. In the other kind the loss of water is accompanied by the loss of an equivalent quantity of sodium, the chief source of the water and sodium being the extracellular fluid, if severe enough, this leads to a bodily disturbance characterised by circulatory disturbances but not by thirst.

The confusion associated with the term dehydration has been increased by each new classification of the disturbance which has appeared. Marriott (1947) wisely suggested that the best solution might be to drop the use of the word 'dehydration' and instead to speak in terms of such causes of disturbance as water depletion, salt depletion or combined water and salt depletion. Pure water depletion corresponds to primary or simple dehydration and affects chiefly though not always entirely the intracellular fluid. Pure salt depletion corresponds to 'secondary" or 'extracellular' dehydration and indicates a reduction in the volume of extracellular fluid. In the succeeding years, as our knowledge of

these disturbances has increased, it has been recognised that sodium depletion is the most important factor in what was formerly called salt depletion (Table VIII)

TABLE VIII

Classification of Dehydration

Pure "water depletion" = "primary" or "simple" dehydration
affects chiefly intracellular fluid
∴ mainly potassium and water lost.
THIRST OLIGURIA.

Pure "salt depletion" = "secondary" or "extracellular" dehydration
affects chiefly extracellular fluid.
mainly sodium and water lost.
CIRCULATORY DISTURBANCES

The effects of deprivation of water on normal subjects has been described by Nadal *et al.* (1941). when the intake of food and water was stopped for three days the body weight fell steadily, the daily urine volume fell to about 600 ml, but its specific gravity rose to about 1036. There was no change in the concentration of sodium in the plasma or in the packed cell volume, but the non-protein nitrogen content rose, the mouth and throat became very dry and thirst was intense. When water was given, recovery was rapid, the weight rose, there was a diuresis and the urine specific gravity and the plasma non-protein nitrogen concentration fell. The excretion of sodium in the urine fell while the intake of food and water was stopped, but that of potassium continued unchanged. Nadal *et al.* (1941) also produced sodium depletion in two normal subjects by duodenal suction with a Miller-Abbott tube, the intake of food was stopped but they were allowed to drink water freely, and water was also given as glucose solution by intravenous infusion. In three days weight loss amounted to 6 and 8 per cent of body weight in the two subjects respectively, and more than 8 g. (348 mEq.) of sodium were removed by suction The serum concentrations of sodium and chloride fell, the packed cell volume and plasma protein concentration rose, but the urine volume remained high at an average of 1430 ml per day Towards the end of the period of suction both subjects became weak and apathetic, they fainted when they sat up and their systolic blood pressure was only 85 mm. Hg. There was marked loss of appetite,

n depletion in surgical practice is that caused by the rapid f large volumes of intestinal secretion, for example in associa ith acute obstruction high in the small intestine. The lost ions are initially derived from the blood plasma which is ished from the interstitial fluid. The composition of the ions which may be lost is shown in Table IX, but in acute of large volumes the important disturbance is the large ion in sodium and water which leads to a depletion of extra- ir fluid volume. The best and most severe example of oss is that associated with Asiatic cholera but very rapid

TABLE IX

Composition of Intestinal Secretions

cretion	*Concentration in mEq per litre*				*Volume per Day (ml.)*
	Na^+	K^+	Cl^-	HCO_3^-	
ic	50	10	150	—	2 500
rnal	140	10	100	25	3 000
y	140	5	100	30	500
eatic	140	5	70	70	700
asma	140	5	103	25	—

in the body, or the adequacy of treatment, except so far as concerns water intake When water is supplied, urine is excreted freely until the continued extrarenal loss of sodium causes a critical reduction in extracellular fluid volume, blood pressure falls and glomerular filtration is reduced. In water lack the urinary volume is frequently lowest on the first day of deprivation and is not a good index of the degree of water loss. Continued use of gastric aspiration after operation has been justified by many surgeons on the grounds that any sodium which is removed in the aspirations is replaced by the intravenous infusion of isotonic saline During any period of aspiration which is really necessary because of accumulation of fluid and blood in the gastric remnant, restriction of drinking will reduce the volume of fluid lost to small quantities which do not require replacement by saline infusions The relief of post-operative thirst is another problem which has already been discussed (see p. 27)

The confusing effects of apparently simple disturbances, and the complications introduced by equally simple remedies, are well illustrated by the effects of excessive sweating. The sodium and chloride concentrations in sweat vary, but are seldom more than half their concentrations in extracellular fluid and may be very low. Sweat therefore removes more water than sodium or chloride, and a single period of sweating leads to a disturbance dominated by the features of water loss. When there are repeated losses of sweat, and these are consistently replaced by water without the addition of any sodium, the accumulated small daily unreplaced sodium losses lead to sodium deficiency, and this may be aggravated by the dilution superimposed by drinking water. Repeated sweating, by causing sufficiently large loss of sodium, thus leads to circulatory collapse instead of simple water depletion. The close resemblance of "heat exhaustion" and the sodium depletion induced by gastric aspiration combined with the free consumption of water, and the chances of a combination of these effects in surgical patients in hot climates, are evident Water depletion results from the restriction or stoppage of water intake or when, following the loss of gastric and intestinal secretions, the replacement of sodium is adequate and that of water is not. Sodium depletion results when both sodium and water are lost and water alone is adequately replaced.

Sodium Depletion. By far the most important form of

sodium depletion in surgical practice is that caused by the rapid loss of large volumes of intestinal secretion, for example in association with acute obstruction high in the small intestine. The lost secretions are initially derived from the blood plasma, which is replenished from the interstitial fluid The composition of the secretions which may be lost is shown in Table IX, but in acute losses of large volumes the important disturbance is the large reduction in sodium and water which leads to a depletion of extra cellular fluid volume. The best and most severe example of such loss is that associated with Asiatic cholera, but very rapid

TABLE IX

Composition of Intestinal Secretions

Secretion	*Concentration in mEq per litre*				*Volume per Day (ml.)*
	Na^+	K^+	Cl^-	HCO_3^-	
Gastric	50	10	150	—	2,500
Intestinal	140	10	100	25	3 000
Biliary	140	5	100	30	500
Pancreatic	140	5	70	70	700
Cf. plasma	140	5	103	25	—

reduction of extracellular fluid volume also occurs in acute dilatation of the stomach acute obstruction of the small intestine, from fistulas of the small intestine, in ulcerative colitis, and by diarrhoea from an ileostomy Less rapid but equally severe loss may follow repeated gastric aspiration after partial gastrectomy

Reduction in sodium intake is rarely the cause of sodium depletion in normal people because renal conservation of sodium is so effective. A low sodium intake may be an important contributory factor in fever or in patients who for prolonged periods lose sodium in discharges from extensive wounds or granulating surfaces The combination of a low sodium diet with the use of mercurial diuretics is dangerous in liver and cardiac disease and in ulcerative colitis with oedema and is liable to cause acute sodium deficiency Sulphanilamide impairs the absorption of sodium by the renal tubules and should not be combined with a low sodium diet (Schwartz, 1949) In chronic loss of sodium the sequence of

events may be obscured and the onset of clinical disturbances may be delayed by the mobilisation of sodium from bone. Chronic sodium loss also causes more complete reabsorption of sodium by the renal tubules and the urinary output of sodium falls. In sodium depletion of normal subjects, McCance (1936) found the sodium deficit was at first parallel to the weight loss, indicating the maintenance of the sodium concentration in extracellular fluid at the expense of the volume of that fluid Later the loss of weight was slower than that of sodium, indicating that extracellular fluid volume was being maintained at the expense of extracellular sodium concentration.

Clinical Features.—The loss of sodium and water reduces the volume of extracellular fluid and plasma volume, but direct measurement of these reductions is seldom practicable and diagnosis depends on observation of the characteristic clinical features A detailed history of the nature and quantity of fluid lost is of first importance The reduced plasma volume is accompanied by increases in plasma protein and haemoglobin concentrations, and in packed cell volume and blood viscosity, which may mask pre-existing anaemia or reduction in plasma protein concentration. Peripheral vasoconstriction compensates for reduction in the circulating volume of blood, but the systolic and diastolic blood pressures may be lowered and the pulse rate may be fast The peripheral veins are small and constricted and poorly filled with sluggishly flowing dark blood The tongue is dry, hard and reddish brown in colour, but the patient is usually not thirsty. The eyes are sunken in deep dark sockets, the face is drawn and the expression may be anxious The skin is wrinkled and dry and the subcutaneous tissues feel lax. The patient often appears to have aged by many years in a few hours The urine is scanty, dark in colour and of high specific gravity This is the state frequently called "dehydration", but it is most important to recognise that it is due to the loss of extracellular fluid and in particular of sodium and water The chemical changes in the blood are subject to wide variation and are seldom of much immediate value in determining treatment, but may be of assistance later in judging the success of treatment The plasma sodium concentration may not be altered by an acute loss of intestinal secretions, and the body deficit of sodium may become obvious only when lost fluid is replaced with solutions containing

small concentrations of sodium The plasma concentrations of chloride and bicarbonate should be measured, as well as that of sodium, since the losses of these radicles vary according to the level in the alimentary tract which is involved

Treatment—No matter what the cause, the first step in the treatment of severe extracellular dehydration must be to ensure survival by restoring the circulating blood volume In some patients this may require the rapid infusion of a plasma substitute followed by isotonic saline. As soon as possible the fluid loss must be stopped or reduced to a safe rate, if necessary by operation

It is often difficult to decide how much of the fluid loss should be replaced before operative treatment is carried out, and to a large extent this must depend on individual circumstances In acute intestinal obstruction the bowel above the point of obstruction is usually distended and inflamed When in addition to restoring circulating volume with a plasma substitute, crystalloid solutions such as saline are injected, there is often a visible and measurable increase in abdominal distension. This is due to the rapid loss of the infused non colloid solutions into the lumen of the inflamed obstructed bowel and the resulting increase in intestinal contents hampers subsequent operative manipulations of the bowel. In most cases of acute intestinal obstruction restoration of the circulating blood volume is all that should be done before operation. The management of more chronic losses of intestinal secretions involves consideration of losses of potassium, and of chloride and bicarbonate, and is dealt with in detail later (see p 145)

When operation is not required, treatment should be directed to replacing the lost fluid as accurately as possible. The most important part is the replacement of sodium and water, and ideally this should be accompanied by appropriate proportions of anions. In general however, acute losses can be satisfactorily replaced by isotonic (0·9 per cent.) saline, and provided renal function is satisfactory and the water intake is adequate, renal compensation will remove any excess of chloride which is administered. In controlling such replacement the best guide is its effect on the general state of the patient and the subsidence of the clinical features which have been described. The most valuable indications are the systolic and diastolic blood pressures the state of filling of the peripheral veins and the packed cell volume or haemoglobin concentration.

It has been suggested that the fluid requirements can be calculated from the alteration in plasma specific gravity, packed cell volume or haemoglobin concentration (Phillips *et al*, 1950). It is probably wiser, however, to judge the volume of fluid directly from the response which is obtained in the individual patient rather than to administer an arbitrarily calculated volume which does not allow for variation in fatness and lean tissue mass It is unwise to try to judge the quantity of sodium or chloride which should be administered from the combination of measurements of their concentrations in the plasma and estimates of the normal extracellular fluid volume of the patient calculated from body weight. The concentration of these ions in extracellular fluid is preserved by several mechanisms at the expense of the volume of the extracellular fluid, and an altered concentration is of most value as an indication either of failure of these compensatory mechanisms or of dilution by excessive administration of water. The degree to which movement of sodium out of bone compensates for losses of sodium from extracellular fluid is unknown. The large quantity of exchangeable, and therefore available, bone sodium and the surprising constancy of extracellular fluid sodium concentration, in spite of large losses of sodium in intestinal secretions, suggests that bone sodium is an important second line of defence in the maintenance of the constancy of the composition of the extracellular fluid

Water Intoxication.—The wider recognition of the sodium retention which normally occurs during the early post-operative period has led to a tendency to administer isotonic glucose solutions instead of saline at this time Even this is not without danger because, during the first week after operation, the excretion of water is slower than normal, and when large volumes of glucose solution are injected rapidly a large proportion of the injected water may be retained and may cause a state of water intoxication. This adverse effect of the excessive administration of water has been recognised for many years and is not confined to surgical patients In chronic disturbances the concentration of sodium may be much more markedly depressed than in water intoxication, without causing any obvious ill-effects. Water intoxication has been described after rectal administration of water (de Takats, 1931) and after excessive drinking of water in the immediate post-operative period. A similar disturbance may follow when sodium

depletion by vomiting or diarrhoea is treated by infusions of sodium free solutions or when vomiting patients are allowed to drink water too freely (salt depletion syndrome Peters, 1948) In cardiac disease it may be associated with the use of mercurial diuretics and a low salt diet combined with an excessive fluid intake (low salt syndrome Schroeder, 1949) The rate at which water is consumed or injected seems to be the critical factor in causing a rapid dilution of the extracellular fluid and its sodium concentration, especially when combined with an inability of the kidneys to remove the added water by a rapid diuresis.

Clinical Features —This disturbance may occur without sodium loss, especially if water intake is rapid. It is commoner after the age of 50 years and when renal function is impaired, it has been observed in the neonatal period in severe infections and after operation (Wilkinson unpublished observations) There is usually a marked gain in body weight at a time when normally weight would be lost. Symptoms and signs usually appear within 48 hours, often after only 24 hours and may follow the administration of as little as 3 or 4 litres of glucose solution in 24 hours (Zimmermann and Wangensteen, 1952) In the early stages there are anorexia, weakness and apathy, later there may be nausea and vomiting or diarrhoea, rapid and stertorous respiration, mental confusion and irritability, twitching of the limbs, epileptiform seizures and coma which may last an hour or two or for days. There are no constant neurological disturbances, but amnesia is usual The plasma sodium, bicarbonate and chloride concentrations are depressed, potassium also is usually reduced, but may be high when renal function is severely affected, the haemoglobin and plasma protein concentrations and packed cell volume are markedly lowered. At first there is a diuresis and a large volume of dilute urine is passed but this is followed by oliguria or even anuria, and sweating stops Oedema is not common and is often most noticeable in the eyelids (Brown *et al*, 1943)

Treatment —During spontaneous recovery the waterlogged patient may lie in an irritable confused state for a week or more, while the excess water is removed by vaporisation and excreted as urine recovery is slow when urinary excretion is reduced by functional changes in the kidneys and may then be accelerated by the intravenous injection of hypertonic saline (5 85 per cent.) Only a small volume (200 to 400 ml) should be slowly administered

and the injection should be stopped as soon as symptoms are relieved or if urinary output increases before all the fluid has been given. A too rapid injection of hypertonic saline may cause sudden cardiac arrest or circulatory overloading. It is thought that hypertonic saline acts by increasing the extracellular sodium concentration, thus restoring the original cation equilibrium at the cell membrane and leading to the extrusion of water from the cells and to the restoration of normal water equilibrium and cellular function.

Oedema.—There is now some support for the belief that the water of the interstitial fluid and of connective tissue is normally in the gel phase of a gel-sol state. If this normal interstitial gel structure becomes supersaturated, the breaking up of the gel phase to a sol leads to the appearance of recognisable pitting oedema. This idea of a gel-sol structure in the interstitial fluid may seem to impose a limitation on the free movement of fluid in this area; this is likely to be apparent rather than real because changes in saturation are constant and lead to the undetectable but repeated breaking up and reformation of the gel on a minute individual scale but in a vast number of situations.

In oedema there is usually also an accumulation of an abnormally large amount of fluid in the tissue spaces which may be due to various disturbances of the mechanism of fluid exchange. Oedema may appear when the movement of fluid into the interstitial space exceeds the removal of this fluid back into the venous capillaries or by the lymph channels; or it may be due to the widespread blockage of lymph channels. It is often difficult to explain the occurrence of oedema in surgical patients Low concentration of the plasma proteins, especially of albumin, should always be considered; this may be the result of malnutrition before operation, or of protein depletion by prolonged losses of exudate from extensive granulating surfaces after burns or other injuries, or from large abscess cavities. Reduction in plasma protein concentration may also be due to dilution of the protein by an increase in extracellular fluid volume. This is often due to an increase in the quantity of sodium in the body accompanied by water retention, without alteration in the extracellular sodium concentration. Retention of sodium may be caused by inadequate renal function following renal disease or by the administration of cortisone. It may also, and more commonly,

be due to the excessive administration of saline during the immediate post-operative period, when the renal excretion of administered sodium is delayed by the normal post traumatic conservation of sodium Stewart and Rourke (1942) found that after even minor gynaecological operations there was retention of a large proportion of the sodium administered intravenously as saline, with expansion of the extracellular fluid volume and reduction in the plasma protein concentration Moyer *et al* (1947) studied the effects of the rapid intravenous infusion of large volumes of isotonic glucose solution and saline in two normal men Five per cent. glucose solution equal in volume to 1 per cent. of body weight was infused at a rate of 740 or 800 ml per hour, within three hours the rate of excretion exceeded the rate of infusion which lasted for five hours, a volume of urine equal to the total volume infused had been excreted within one hour of stopping the infusion. When similar quantities of saline were administered to the same subjects the urine flow rose slowly to a peak of 200 to 300 ml per hour at two hours and then fell towards the initial rate, at the end of the infusion 75 per cent of the infused volume had not been excreted.

So-called ' starvation oedema may occasionally be found in surgical patients, especially in those with slowly progressive obstructions of the oesophagus or intestines or ulcerative colitis, in the latter disease it may be exaggerated by treatment with cortisone or ACTH It is due to the close conservation of sodium by the kidneys with consequent maintenance of a nearly normal total body content of sodium and volume of extracellular fluid in spite of large reductions in cell mass and total protein and potassium contents

Excessive accumulation of extracellular fluid does not always cause recognisable oedema, large quantities of fluid may accumulate before there is pitting on pressure even in dependent parts such as the sacral region the scrotum, or the feet and legs Crepitations in the basal regions of the lungs are probably more often due to retention of bronchial secretions than to hydrostatic oedema of the lungs Provision must be made for the continuing insensible loss of water and for urine formation It is important to remember that although oedematous patients have an excessive quantity of extracellular fluid they may at the same time be losing intracellular fluid and potassium The intracellular dehydration

causes thirst and a dry tongue; sufficient water to relieve thirst should always be provided. This water is unlikely to increase the oedema which is due to retention of sodium, but by maintaining urinary output will help to remove sodium if this is within the capacity of the kidneys. Sodium excretion may also be promoted by the use of a mercurial diuretic. The intake of sodium should be reduced, but the value of a low sodium diet is doubtful, especially in convalescent surgical patients, this diet is tasteless and many patients find it unattractive and difficult to consume. The resulting inadequate calorie intake prolongs the catabolism of protein tissues and accentuates existing protein deficiency. Some reduction in body sodium content may be achieved by the use of a suitable cationic exchange resin, and by reducing sodium absorption such a resin may permit the consumption of a more palatable diet of higher sodium content than would otherwise be safe. The effectiveness of a mercurial diuretic seems to be increased when it is combined with the consumption of a resin, but there is a danger of acidosis when renal function is impaired.

CHAPTER III

POTASSIUM

NORMAL CONTENT AND DISTRIBUTION

NEARLY 98 per cent (3360 mEq) of the potassium in the body is in the cells, three-quarters of it being in the skeletal muscles, and only about 2 per cent. of the total (60 mEq) is in the extracellular fluid. Whereas sodium forms 90 per cent of the total cations of the extracellular fluid, potassium although the predominant cation of intracellular fluid accounts for only two-thirds of the total

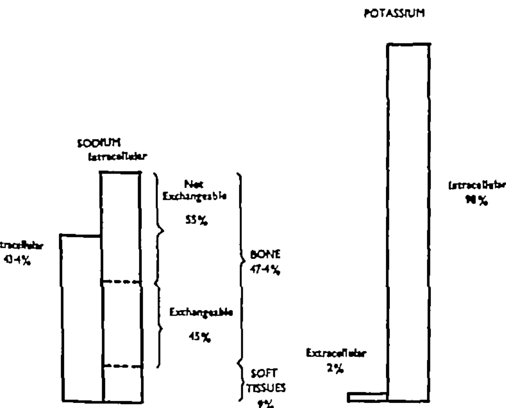


FIG. 3 —Comparison of distribution of sodium and potassium.

active intracellular cations, the remainder being magnesium (Fig 3). For many years potassium has been used in metabolic experiments as an index of change in intracellular fluid volume.

INTAKE AND OUTPUT

Each day a healthy adult consumes about 2 to 3 g. (52 to 78 mEq.) of potassium and about 2 to 3 g. are excreted in the urine and a very small quantity in the faeces and sweat. In addition, from 2 to 5 g. (52 to 130 mEq.) are secreted into and reabsorbed from the alimentary tract every day (Table X).

TABLE X

The Daily Potassium Cycle

Consumed in ordinary diet	2-3 g (52-78 mEq)
Excreted in urine	2-3 g (52-78 mEq.)
Secreted into and reabsorbed from gastro-intestinal tract	2-5 g (52-130 mEq)
Lost in sweat . . .	trace
Lost in faeces	less than 10 mEq.

COMPARISON OF SODIUM AND POTASSIUM METABOLISM

One of the striking differences between sodium and potassium lies in the ways in which these ions are treated by the kidneys. Sodium appears to be under careful control at all times; any excess of intake is excreted in the urine, although there may be delay in doing this after injury and in the presence of infection; any deficiency of sodium is followed by the close renal conservation of the remainder in the body, the urinary loss being reduced to a very small quantity, and in this way the sodium concentration in the extracellular fluid and the total quantity of sodium in the body are preserved. Potassium is obtained from the food, and after absorption is transported from the intestine to the cells by the extracellular fluid. The rapid uptake of this absorbed potassium by the cells prevents any increase in the concentration of potassium in the extracellular fluid When, because of some generalised cellular disturbance, there is a generalised shift of potassium out of cells, there is a tendency for the potassium content and concentration of the extracellular fluid to rise. Usually this is dealt with by the kidneys, which excrete the potassium in the urine sufficiently fast to maintain the concentration of potassium in the extracellular fluid within the normal adult limits of 3·8 to 5 1 mEq. per litre (15·0 to 20 0 mg. per 100 ml.) The total quantity of

ium in the extracellular fluid is about 60 mEq During ition and when after injury protein tissue is catabolised, large ities of potassium are released from catabolised tissues, in ition, for example, 10 to 12 mg (2 5 to 3·0 mEq) (Benedict, of potassium are released with every gram of nitrogen Even y 6 g of nitrogen, equivalent to 37 5 g of protein, or 180 g sh muscle, are destroyed each day, the extracellular potassium nt would be doubled in four or five days. Although the total itties released each day decline as the fast proceeds and in catabolism diminishes, excretion of potassium by the y must continue if the extracellular fluid concentration is to pt within normal limits.

description will be given (see Figs 6 and 7) of the large ase in urinary potassium excretion which normally occurs n 48 hours of injury and is presumably accompanied by llows the mobilisation of water from the cells and pre- i the excretion of a large quantity of nitrogenous material. It not seem unreasonable to imagine that this large mobilisa of cellular potassium and water is in some way connected with apacity of the organism to survive injury without external especially as this response to injury is not modified by the inistration of water Yet survival also depends on the ability ie kidneys to conserve sodium and thus preserve a sufficient me of extracellular fluid to allow the transport of oxygen and ces of energy to the cells and the removal of the products of llar metabolism and destruction In patients with anuria the mulation of potassium in the extracellular fluid raises its entration to a toxic level which is probably the commonest e of death in this condition. Thus survival depends jointly on ability of the kidneys to conserve sodium and to excrete ssium. Because of this continuing loss of potassium in the e, the body content of potassium falls when the intake is iced or stopped by starvation or restriction of the diet, or by uting and also when the output is largely increased by the of intestinal secretions. Potassium excretion in the urine is eased by the administration of ACTH, cortisone, desoxy- icosterone, aldosterone, PAS and mercurial and other diu- s such as chlorthiazide, and by the intravenous administration solutions containing sodium salts, glucose or ammonium ride.

The normal daily output of potassium in the urine ranges up to 2 to 3 g. (52 to 78 mEq.) and is related closely to the dietary intake It is impossible to say what proportion of the urinary potassium is derived from unabsorbed filtrate and how much is due to tubular secretion. Berliner *et al.* (1950) came to the conclusion that the excretion of potassium in the urine was largely independent of its plasma concentration and the glomerular filtration rate, which accords well with the large urinary output of potassium in high concentration so often found after even very severe injury. The independence of potassium excretion of any relationship with that of sodium can be illustrated in many ways, Stanbury and Thomson (1951) found on a rice diet that not only was potassium excretion independent of large changes in glomerular filtration rate but that the usual morning rise in potassium excretion occurred when sodium excretion was negligible. In some way the urinary excretion of potassium is related to the state of cellular economy as that of sodium is related to extracellular fluid economy.

Evidence from depletion experiments in normal subjects led Fourman (1952) to suggest that there is some renal conservation when large quantities of potassium are lost from the body. Lowe (1953) has reported experiments in which he fed an electrolyte-free diet consisting of 300 g. glucose and 150 g. arachis oil, emulsified in a total volume of one litre, and containing an adequate vitamin supplement. In just over three days the urinary excretion of potassium fell from 65 mEq. per day to under 10 mEq. per day and remained thereafter at a low level. Urinary sodium and chloride also fell, but the plasma chemistry remained within normal limits. This mixture provided an adequate intake of energy, and the low urinary urea output indicated that tissue protein was not catabolised to any great extent. It might be inferred from these results that renal conservation of potassium was good because the urinary output of potassium, like that of sodium, fell markedly when the intake was reduced. It seems as reasonable to conclude, however, that since the intake of potassium was stopped and tissue catabolism was almost completely prevented by the high caloric intake, there was little potassium to be excreted. This does not mean that renal conservation of potassium is good in these circumstances but bad when, following severe injury and in the absence of a supply of calories and water, the

kidneys excrete large quantities of potassium at a high concentration in the urine.

Whether potassium is excreted in the urine seems to be determined by how much there is available for excretion in the extra cellular fluid, and on whether cells are shedding or retaining potassium, which depends in part on the events to which the body has recently been subjected and their effect on cellular and whole body metabolism Restriction of water intake does not alter the total daily requirements of water for insensible loss, although it does affect urinary volumes At least part of the obligatory water expenditure is derived from intracellular fluid and may lead to the mobilisation of potassium from the cells and to its transfer to the extracellular fluid before it is excreted in the urine Starvation for food leads to catabolism of tissue protein and fat to provide energy for continuing metabolism Injury induces a complex chain of circumstances which include tissue catabolism whether food is supplied or not Tissue catabolism releases potassium from cells into extracellular fluid. Clearly it must be an important function of the kidneys to get rid of potassium from the body when there is any tendency for the potassium content of the extra cellular fluid to rise The rate of urinary excretion of potassium seems to depend partly on the effect of external agencies (injury starvation water restriction) on cellular and whole body economy, and partly on the efficiency with which the kidneys can maintain the extracellular fluid as an environment fit for cells to live in if these views are sound then the term conservation cannot be applied to the renal treatment of potassium in the same sense as for sodium.

The measurement of the total body content of potassium is not yet generally practicable, since it involves the use of radioactive potassium. It has been suggested that measurement of the potassium content of the red blood corpuscle would serve as an index of the intracellular potassium this has proved disappointing because it has been found that the red cell potassium content does not reflect the general cell state, and under circumstances of acute alteration in potassium content change in the red cells lags behind the rest of the body (Corsa *et al* 1950) The potassium content of skeletal muscle biopsies can be readily measured, but it is necessary to apply corrections for the quantity of extracellular fluid in the muscle, this is most difficult and unreliable in just

those circumstances of body fluid disorder in which the estimation would be of most value. It is possible to compare the potassium and sodium contents of fat-free dried biopsy specimens of skeletal muscle with those of normal muscle and so to get some idea of whether the values lie within the normal limits and ratios, but the total body content of potassium cannot be measured in this way. The only really practicable means of measuring potassium deficiency is by measuring the degree of retention of administered potassium when a deficiency is being replaced. In this connection it is well known that during the administration of potassium salts after depletion the urinary output of potassium may not rise and may even fall in spite of an elevation in the potassium concentration of the plasma.

PLASMA POTASSIUM CONCENTRATION

The normal range of potassium concentration in the plasma is from 3·8 to 5·1 mEq. per litre (15·0 to 20·0 mg. per 100 ml.), and values of less than 3·5 mEq. (13·6 mg. per 100 ml.) or more than 7 mEq. per litre (27 mg. per 100 ml.) are usually considered to be abnormal. The concentration at a particular moment depends on the rate at which potassium is being mobilised from or deposited in cells or excreted in the urine, and also on changes in the volume of the extracellular fluid. Although the total body content is normal, the serum potassium concentration may be reduced when the extracellular fluid volume is rapidly increased by intravenous infusions, or by the rapid deposition of glycogen after the administration of glucose and insulin, or in patients who are being treated with adrenal cortical hormones and are excreting potassium in the urine more rapidly than it is being mobilised from the cells The serum potassium concentration may be raised in spite of a large body deficit of potassium when the extracellular fluid volume is reduced, for example by loss of intestinal fluids, especially if renal function is impaired or the output of urine is reduced. Persistent depression of the serum concentration is usually a feature of severe and prolonged potassium deficiency, whereas elevation of the concentration is most often found in association with renal failure or anuria.

The interpretation of the serum potassium concentration is difficult. The typical 70 kg. adult male with a total potassium

content of 3400 mEq would have only 60 mEq of potassium in his 12 litres of extracellular fluid and 15 mEq in 3 litres of plasma (equivalent to the potassium in only 1 2 g potassium chloride) The plasma concentration can be raised by 50 per cent. from 5 to 7 5 mEq per litre by altering the distribution of only 30 mEq of potassium, less than 1 per cent of the total body content and roughly equivalent to the potassium content of half a pound of beef When an abnormal serum concentration is found, the measurement should be repeated and the daily intake and urinary and other outputs or losses of potassium should be measured and if possible sodium and water exchanges also should be measured When it has been possible to measure the total exchangeable potassium by the isotope dilution method, deficiencies of up to 1000 mEq of potassium, one-third of the normal body content, have been found in chronic malnutrition and in prolonged pyloric stenosis, such huge deficiencies are not always accompanied by low serum potassium concentrations

POTASSIUM DEFICIENCY

The maintenance of a normal content of potassium in the body depends on the steady daily intake of a sufficient quantity of potassium in food Because the kidneys do not deal with potassium in the same way as sodium excretion of potassium in the urine continues under all circumstances save anuria, and when the intake of food is restricted or ceases this continuing urinary loss leads to slow depletion of the body content of potassium.

Types of Potassium Loss —Broadly speaking there are two main modes of loss of potassium from the body

1 *Proportionate loss of potassium* and nitrogen occurs in starvation without restriction of water intake. As the result of the catabolism of protein tissue potassium and nitrogen are excreted in the urine in proportions closely resembling those in which they are found in a typical protein such as skeletal muscle (2 5 to 3 0 mEq potassium per gram of nitrogen) In recovery from starvation, nitrogen and potassium are retained in the body in the same proportions

2 *Disproportionate loss of potassium* in comparison with nitrogen occurs in intracellular dehydration. This consists in the outward movement of potassium and water from the cell into the extracellular fluid and then into the plasma, from which potassium is

excreted in the urine The result is a loss of water and potassium from the body. This type of loss provides a means of supplying limited quantities of water for various purposes. Gamble (1954) has shown that when the intake of water as well as of food is stopped, within 48 to 72 hours renal conservation reduces to a very low level the urinary loss of sodium and thus of extracellular fluid, and thereafter the main endogenous source of water is the intracellular fluid, as is shown by the steady excretion of potassium in the urine. A disproportionate loss of potassium also occurs when gastro-intestinal secretions are lost from the body, and this type of fluid loss also leads to intracellular dehydration The intravenous administration of 0 9 per cent saline or of 5 per cent. glucose solution, even to normal subjects, leads to an increased output of potassium in the urine; the administration of these fluids to surgical patients is an important factor in increasing potassium depletion. When a large volume of glucose solution is rapidly infused, the resulting water diuresis usually continues longer than is necessary to excrete all the added water, and some degree of water depletion occurs; this in turn leads to the movement of water out of cells with the transfer of potassium from cells to extracellular fluid. When saline is infused, it makes little contribution to the water requirements of the body, since even normal kidneys can concentrate saline and free water from it only to a limited extent, water is then obtained by the mobilisation of intracellular fluid with excretion of potassium in the urine.

The concentration of potassium in the gastro-intestinal secretions may be up to twice that in the plasma, whereas the concentration of sodium never exceeds and may be less than that in plasma. In acute losses of gastro-intestinal secretions the lost fluid resembles in composition and is derived from the plasma and extracellular fluid, but usually contains more potassium than these fluids. This loss of potassium is replenished from the intracellular fluid. In acute losses of short duration, because of the low extracellular fluid concentration of potassium, only about 4 per cent. of the total body potassium may be lost, but up to 25 per cent. of the total available extra-skeletal sodium may be lost. In the treatment of such acute losses of gastro-intestinal fluids the initial emphasis is rightly on the replacement of extracellular fluid, and is satisfactorily achieved by the intravenous administration of sodium and water as isotonic saline Provided that the

consumption of a normal diet is then resumed, the relatively small loss of potassium will be made good from dietary potassium However, when there is prolonged vomiting with restricted food intake, or when in gastro-enteritis there is loss by vomiting and in fluid stools together with restriction of intake the losses of potassium are repeated There may be replacement of the sodium and water by saline infusion, but *if potassium is not also replaced* the total loss may eventually amount to as much as 25 per cent of the original potassium content of the body The importance of replacing this potassium loss was first shown by Darrow (1946) By adding the administration of potassium chloride to the ordinary treatment he reduced the mortality in infants suffering from gastro-enteritis from 17 deaths in 53 patients to only 3 in 50 patients He showed also by carrying out nitrogen and potassium balance estimations during treatment and the recovery period that these young children retained more potassium than would have been expected from the nitrogen balance. This means that more potassium was retained in the body than the quantity required in combination with nitrogen (2 5 to 3·0 mEq potassium per gram of nitrogen) to reform the catabolised tissue protein In other words, potassium lost in the intestinal secretions during the period of vomiting and diarrhoea, and in the urine was derived from intracellular fluid. Only very small quantities of potassium and sodium are lost in normal formed stools and there is usually more potassium lost than sodium Darrow found that in watery stools the loss of both sodium and potassium was large and that that of sodium was the greater

Darrow *and his colleagues* (Darrow and Pratt 1950 Cooke *et al.* 1952) have produced evidence that when potassium is lost from the cells it is replaced in part by sodium and hydrogen ions in the proportion of two sodium ions and one hydrogen ion for three potassium ions. When potassium is replaced in the cells the sodium and hydrogen ions are equivalently displaced by the potassium. This substitution of sodium and hydrogen for intracellular potassium reduces the otherwise great disturbance in cellular function which would result from the loss of up to 25 per cent. of the body potassium and its associated water from the cells, but does not entirely prevent distortion of the normal equilibrium between intracellular and extracellular fluid At the same time the transfer of sodium into the cells may reduce the total extracellular

cation and the volume of extracellular fluid, especially if the intake of sodium is restricted or the output or loss is excessive. The shift of hydrogen ion from extracellular to intracellular fluid leads to an extracellular alkalosis and intracellular acidosis which are corrected only when the primary disturbance, the loss of potassium from the cells, is overcome by the replenishment of the body content of potassium This alteration in the content and distribution in the body of both sodium and potassium causes disturbances of function which it is probably wrong to ascribe particularly to the primary loss of potassium although it is probably correct to emphasise the potassium factor in the design of suitable treatment.

Causes of Potassium Deficiency.—In the production of potassium deficiency in surgical patients, any or all of the following factors may be concerned:

1. Restriction or stoppage of intake of food, with cessation of potassium intake combined with continued loss of potassium in the urine;
2. Proportionate loss with nitrogen and other constituents of cellular protoplasm due to tissue catabolism because of starvation or in response to injury;
3. Disproportionate loss (*a*) from cells due to intracellular fluid loss because of inadequate water intake; (*b*) in gastro-intestinal secretions by vomiting, diarrhoea or in fluid lost from intestinal fistula.

The Clinical Features of Potassium Deficiency.—Apart from the continuing daily loss of potassium in the urine, the losses of potassium in intestinal secretions are small compared with those of sodium and water. There is therefore in most cases of severe potassium deficiency a long history of loss of secretions, and this is by far the most important stimulus of the suspicions which lead to accurate diagnosis. The clinical picture varies greatly and is commonly obscured by associated disturbances of sodium and water Black (1953) voiced a widely held opinion when he said that many of the symptoms of potassium deficiency may be found in any severe prolonged illness, and this may be because any severe prolonged illness may cause some degree of potassium depletion. The most effective combination is severe and prolonged illness with repeated and large losses of gastro-intestinal secretions

The most striking feature of severe deficiency is the gradual onset of an intense drowsiness or even coma. The patient lies slumped in bed the head drooping down on one shoulder and the jaw and cheeks hanging slackly he is roused with difficulty and opens his eyes slowly and with obvious effort blinking and screwing up his face, then apparently too tired to go on looking the eyelids drop and he seems to go to sleep again Speech is slow and slurred and he may break off in the middle of a sentence. These patients are often irritable and may suffer much change in personality, but after recovery there is commonly amnesia for several days during the most severe part of the disturbance One patient had been seen by a psychiatrist, so prominent were the mental changes in another, potassium deficiency was recognised after a physiotherapist had complained that the patient was always going to sleep during her exercises a third when asked to put out her tongue did so, but drowsed away again with her tongue still protruding

As well as such profound apathy there may be muscular weakness and rarely even neuromuscular inco-ordination The deep reflexes may be absent There may be difficulty in swallowing with inhalation of food or drinks Incontinence of urine is common, perhaps because the sensation of fullness of the bladder is impaired.

Abdominal distension due to chronic ileus is a common feature of post-operative potassium deficiency, but is uncommon before operation. The potassium depletion causes diminished motility of the intestinal musculature which results in the accumulation of intestinal secretions, this in turn stimulates further secretion and more potassium is thereby lost into the lumen of the intestine. In pyloric stenosis there is accumulation of secretions in the dilated, oedematous and hypertrophied stomach, but the intestines are usually empty and contracted Part at least of the stenosis may be due to muscular inco-ordination or spasm of the pylorus and although this may be due to sodium deficiency it may persist in spite of the infusion of large volumes of saline and be relieved only when potassium chloride is administered

The peripheral blood pressure is lowered the pulse rate is slow and the superficial veins are well filled, the skin is warm and dry, but there may be a reddish flush of the face and the backs of the hands. The blood pressure is reduced also in sodium depletion

with reduction in the extracellular fluid volume, but there is then usually acceleration of the pulse rate and the peripheral veins are poorly filled. The heart may be enlarged and there may be changes in the electrocardiographic tracing, but these vary widely and are not always present even in severe deficiency and do not seem to be closely related either to the severity of the deficiency or to the serum potassium concentration. A large number of changes have been described, including reduction in the magnitude of all waves, increased QT interval, decreased height and inversion or rounding and prolongation of T wave, depression of ST or inversion of P wave. These changes may be produced by alkalosis and changes in blood *p*H as well as by potassium deficiency (Nadler *et al.*, 1948) When they are due to potassium deficiency, there is usually improvement after the administration of potassium salts.

The plasma potassium concentration is not always reduced and may sometimes be raised

The specific gravity of the urine is low and renal clearance is depressed because of reduction in both glomerular and tubular functions. Schwartz and Relman (1953, 1956) have shown that these functional disturbances can be related to the histological appearances of vacuolation of the epithelium of the proximal tubules, and that these changes disappear when the potassium deficiency is corrected. The changes they have observed in biopsies of human kidneys are similar to those first described in the kidneys of potassium-deficient rats by Schrader *et al.* (1937).

Diagnosis of Potassium Deficiency.—Potassium deficiency should be suspected and looked for whenever there has been prolonged loss of gastro-intestinal secretions and severe restriction of food intake, and especially when there is severe alkalosis. In these circumstances it is also predisposed to by the intravenous administration of fluids which do not contain potassium, especially when such treatment is the only source of water and calories. The history and the clinical appearance are the most certain means of making the diagnosis; a low plasma potassium concentration and typical alterations in the electrocardiographic tracing are valuable confirmatory evidence but are seldom the only signs of deficiency, nor should great emphasis be laid on these investigations. It is important to remember that the plasma potassium concentration may be low in the absence of the characteristic symptoms and

signs of deficiency, and that not all cases of severe deficiency are consistently associated with depression of the potassium concentration in the extracellular fluid In slowly advancing depletion the plasma concentration usually falls only when the total loss is very large. The very rapid loss of intestinal secretions, containing two or three times as much potassium as the extracellular fluid, may cause acute depression of the plasma potassium concentration which is rapidly restored from the cells when the fluid loss diminishes or ceases, especially if there is oliguria.

Treatment of Potassium Deficiency —The replacement of a large deficit of potassium involves the administration of sufficient potassium and its transfer into the depleted cells The common coexistence of alkalosis or acidosis with potassium deficiency also requires that a suitable potassium salt should be chosen In advanced potassium deficiency, sodium and hydrogen which have replaced the lost potassium in the cells are displaced when potassium is once more made available in sufficiently large quantities

The proportion of the total original content of potassium which must be lost before clinical signs of deficiency arise has not been accurately estimated and probably varies to some extent in different people. It is related to the general state of nutrition and to the size of the muscle mass, which contains over 75 per cent of the total potassium in the body The loss of 200 mEq in 2 or 3 days is well tolerated by most patients and is a common event after many major operations such as partial gastrectomy It seems probable that, in adults, losses of up to 500 mEq (19 5 g) do not cause any ill-effects. Elkinton and Tarail (1950) concluded that the potassium deficit may range from 3 8 to 15 6 mEq per kg body weight (286 to 1092 mEq in a 70-kg patient) after loss of gastro-intestinal secretions combined with a low potassium intake, and from 5 8 to 17 3 mEq per kg in infantile diarrhoea. Martin *et al.* (1951) measured the retention of potassium during replenishment of patients depleted of potassium, and concluded that in chronic types of potassium depletion the deficiency amounts to about 1000 mEq In patients with primary aldosteronism Mahler and Stanbury (1956) have reported a potassium deficiency of 1400 mEq and Milne *et al.* (1957) one of 1000 mEq This accords well with Darrow's original observations (1946) that infants with gastro-enteritis might lose up to 25 per cent. of their

initial potassium content. A typical adult weighing 70 kg. (11 stones) contains about 3400 mEq. potassium, 25 per cent. of which is 850 mEq. (33 15 g.) potassium. The loss of a quarter of the body potassium implies the loss also of about a quarter of the intracellular water equal to about 7 5 litres. This water may be lost before or at the same time as potassium is lost but may be in part replaced by the subsequent transfer of water with sodium and hydrogen into the cells. The final result is the loss with potassium of some of the original water content of the body, although this may be masked later by the excessive retention and abnormal distribution of administered water and sodium.

Whenever possible, potassium salts should be administered by mouth because of the danger of rapid increase in potassium concentration in the extracellular fluid which is inseparable from the intravenous administration of solutions of potassium salts; this danger is particularly great when the extracellular fluid volume is reduced by rapid loss of intestinal secretions and when urine output is low. If there is peripheral circulatory failure, the blood volume must first be rapidly restored by the infusion of dextran. It may sometimes be necessary also to administer saline to restore the extracellular fluid volume in general, but in view of the known tendency of sodium to be transferred into the potassium-deficient cells, only a minimum of sodium should be given to patients who exhibit the clinical signs of potassium deficiency.

When the patient is comatose, has difficulty in swallowing or is nauseated, intravenous administration is often unavoidable, and it is fortunate that in many cases the infusion of as little as 1 g. of potassium chloride (containing 13 5 mEq. potassium) may lead to the recovery of consciousness; there may also be an equally rapid improvement in the mental state of irritable and drowsy patients. Because of the risk of raising the extracellular potassium concentration to a toxic level (above 27 mg. per 100 ml. or 7 mEq. per litre) and thus causing cardiac arrest, it is essential to ensure if possible an adequate flow of urine equivalent to 500 ml. per 24 hours (or 20 ml. per hour) If necessary, therefore, 500 ml. of 5 per cent. glucose solution should be administered before the infusion of a solution of a potassium salt is started.

Potassium deficiency is usually accompanied by extracellular alkalosis when the disturbance is due to vomiting or to high small intestinal fistulae, or by acidosis when it is due to diarrhoea or to a

low intestinal fistula When alkalosis is present, potassium chloride should be employed, and provided that the urinary volume is adequate, up to 2 g (containing 27 mEq potassium) should be administered over a period of 4 hours by the intravenous route, using a solution containing 0 55 per cent potassium chloride (74 mEq per litre) *Depending on the clinical state of the patient* a further 2 g potassium chloride may then be given preceded if necessary by 500 to 1000 ml of 5 per cent glucose solution to maintain urinary volume and prevent intracellular dehydration Alternatively, the potassium chloride may be administered dissolved in glucose solution, by having available small bottles containing a sterile 10 per cent solution of potassium chloride, 20 ml *of which are added* to 500 ml of 5 per cent glucose solution.

In the early stages of treatment, up to 12 g of potassium chloride (162 mEq potassium) per day in doses of 2 g every 4 hours, may be administered orally to co-operative patients whose daily output of urine exceeds 500 ml When there is associated acidosis, the intravenous solution should contain sodium lactate in addition to potassium chloride (Darrow's solution), when the patient is able to swallow potassium citrate should be administered by mouth in 2 g doses every 4 hours Alternatively, the mixture proposed by Leonsins (1951) may be used 1 g each of potassium bicarbonate, acetate and citrate, dissolved in 8 ml of water and flavoured with fruit juice being given every 6 hours providing 116 mEq potassium per day Tarail and Elkinton (1949) have advised that in fluids for intravenous administration the potassium concentration should not exceed 70 to 80 mEq per litre, equivalent to 0 5 to 0·6 per cent. solution of potassium chloride they recommend also that the rate of infusion should not exceed 20 mEq potassium per hour, equivalent to 1 5 g potassium chloride per hour, which may be rather too fast to be safe in patients whose extracellular fluid volume is reduced There is some theoretical justification for the use of potassium phosphate as well as potassium chloride, but so far clinical evidence in favour of this is lacking To produce a solution of *p*H 7 35, 4 5 g dipotassium hydrogen phosphate (51·75 mEq potassium) must be combined with 1·0 g potassium dihydrogen phosphate (7 3 mEq potassium)

The total quantity of potassium which is required to overcome the potassium deficiency in any particular patient must be judged by the individual response to treatment. The serum potassium

concentration commonly falls a day or so after treatment has begun, even when saline has not been administered by infusion, and may drop to a very low level during replacement before slowly rising to within normal limits. It is usual for correction of the alkalosis to be achieved some days before potassium replacement is complete The administration of potassium salts should be continued for at least three days after the plasma potassium concentration has returned to within normal limits, and no harm is likely to result from persisting even longer. If treatment is stopped too soon, the disturbance is liable to recur, especially after a subsequent operation. During the period of intravenous treatment up to 6 g. of potassium chloride (81 mEq potassium) should be given in the first 24 hours. Up to 12 g. potassium chloride per day (162 mEq. potassium) in 6 doses of 2 g. at intervals of 4 hours should be given by mouth until the plasma potassium concentration returns to within the normal limits, the total may then be reduced to 8 g. per day (4 doses of 2 g. at intervals of 6 hours) for at least another 3 days, or until a full diet is being consumed. If the patient continues to lose fluid by vomiting, fistula or diarrhoea, more prolonged intravenous administration may be needed. Such continuing losses should be stopped by suitable surgical treatment as soon as possible

The intravenous administration of potassium salts is dangerous and should never be treated as a matter of routine The decision to start an infusion containing an effective concentration of a potassium salt should be taken only after the most careful consideration of the history and clinical state of the patient. The quantity to be given and the rate of its administration should be stated in writing, and the infusion should be closely supervised by a house surgeon When, for example, 2 g. potassium chloride have been infused, the patient should be re-examined before more is administered. Rarely, signs of improvement may then justify cessation of intravenous administration, but usually it is necessary to give 4 to 6 g. by the intravenous route. The best indication of a dangerous rise in extracellular potassium concentration is slowing of the heart and pulse rates, the solution of potassium chloride should at once be replaced by 5 per cent glucose solution With care and close observation, serious complications can be avoided, but the risk of intravenous administration should always be borne in mind and balanced carefully against that of failing to replace

sufficiently rapidly by oral administration alone, the continuing losses of potassium

A few patients are in such an advanced state of potassium depletion when first seen that nothing but the rapid intravenous administration of potassium can save their lives in some of these the administration of potassium appears to be necessary to restart urine formation On the other hand there does not seem to be any indication for the administration of potassium salts during the first week after operation There is good evidence that for at least three days after operation the body is so constituted that the emphasis is on potassium excretion and that infusions of potassium are not of any use Recent suggestions that the daily administration of small quantities of potassium salts during the first week after operation will not do harm and may do some good seem unwise. Potassium salts should be administered only when there is a clear history of severe loss or prolonged deficiency of potassium, or in the presence of clinical signs of deficiency

The remission of symptoms after the administration of potassium salts is not conclusive proof that they were due solely to potassium deficiency because the restoration of the potassium content of the body has effects on other associated abnormalities such as alkalosis The only certain way of judging when a deficit has been fully replaced is by carrying out a potassium balance study during replacement measuring and comparing the daily intake and the output in the urine and any other losses which occur The urinary output usually remains low until replenishment is almost complete, when it rises. When the plasma concentration of potassium is low initially it also usually remains low until replacement is nearly complete Unless a potassium deficit is corrected before operation, the normal post-operative urinary loss of potassium may be sufficient to convert an occult into a manifest acute clinical deficiency state. When there is a history of prolonged loss of potassium it is important to try to replace as much as possible of the lost potassium before operation is undertaken In normal circumstances potassium requirements are fully satisfied by the consumption of a good mixed diet. When only a limited diet is being consumed during convalescence from operations, severe injuries and other extensive inflammations, it is at least theoretically desirable to increase the consumption of potassium. Such well recognised invalid foods as chicken and

beef tea, broth, meat extracts, fruit and fruit juices are good natural sources of potassium in palatable forms, the richest natural source is black treacle The addition of dried milk powder to soups, sauces and custards also increases their potassium content.

POTASSIUM RETENTION

In the healthy subject it appears to be impossible to increase the potassium content of the body to such a degree that the plasma potassium concentration rises above the normal limits. This depends on the ability of the kidneys rapidly to excrete excessive added potassium Elevation of the plasma potassium concentration is not uncommon late in many diseases, and, as food intake is then often reduced or has been stopped, is due to the incomplete excretion of potassium derived from cellular breakdown; this is usually associated with severe oliguria or anuria. It may also be due to the intravenous infusion of potassium salts in excessive quantities or at too fast a rate when urinary volume is low In many reported cases the serum sodium concentration was low. This suggests that reduction in the volume of extracellular fluid is also an important factor in raising the potassium concentration, and that although the plasma and extracellular fluid concentration of potassium may be high, the total body content may be reduced.

Clinical Features of Potassium Retention.—It is difficult and perhaps not justifiable to associate any particular clinical features specifically with a raised plasma potassium concentration. Attention is focused in most cases on the condition underlying the potassium retention, for example anuria or an acute loss of extracellular fluid, and in the latter particularly the raised potassium concentration is often only an incidental discovery. In anuria, progressive increase in extracellular potassium concentration appears to be the commonest cause of death. Electrocardiographic changes are more common with a high than with a low plasma potassium concentration, and are likely to be found when this reaches 7 mEq. per litre (27 mg per 100 ml.) and are always present at 8 mEq. per litre (30 mg. per 100 ml.). The T wave is peaked, and the duration of the QRS complex and the P-R interval is increased. There may also be some mental confusion and apathy, sensory disturbances and weakness of the limbs. The peripheral circulation is poor with cold, pale, cyanosed skin and

low blood pressure the heart rate is slow, the beats are irregular and cardiac arrest may follow

Treatment of Potassium Retention—Success in treatment depends first on preventing any further increase in extracellular potassium concentration, and secondly on the elimination of the accumulated potassium If the accumulation is due to the excessive intravenous administration of potassium salts, the flow of fluid containing potassium must be stopped and the urinary volume and excretion of potassium promoted by the rapid infusion of 5 per cent. glucose solution When associated with oliguria due to water intoxication or sodium depletion, urinary output may be increased by the infusion of hypertonic saline. The treatment of potassium retention in anuria is discussed in detail on p 175

MAGNESIUM

Magnesium is known to be an important factor in the maintenance of normal contractility in muscle and excitability in neural tissue, and to be concerned in the catalysis of several enzymic processes concerned with the storage, transfer and utilisation of energy Very little is known of changes in content and distribution of magnesium in the body during disease, largely because of the difficulties formerly associated with its chemical estimation, now that potassium depletion is being recognised more often and treated adequately and successfully it is at least possible that deficiencies of magnesium which arise in similar ways also may be more often encountered Magnesium is usually considered, from a nutritional standpoint, in conjunction with calcium and phosphorus, because they constitute the major part of the mineral content of bone However whereas almost all the calcium is in the bones or teeth and only about 1 per cent is in the extracellular fluid, both magnesium and phosphorus are important constituents of the intracellular fluid of soft tissues

Amongst the intracellular cations magnesium is next in importance to potassium Baldwin *et al.* (1952) studied the interrelationship of magnesium, potassium phosphorus and creatinine in human skeletal muscle, and concluded that there is a constant potassium magnesium ratio of 5 67 1 in all muscle regardless of the physical state of the subject or the serum potassium concentration. They found a proportional loss of nitrogen, potassium

phosphorus and magnesium from atrophied muscles. The range of concentration of magnesium in the serum of normal subjects was 1 7 to 2 2 mEq per litre (potassium 3 5 to 5 0 mEq. per litre) and in muscle the average content of magnesium was 16 4 mEq per kg. wet muscle (potassium 94 6 mEq per kg wet muscle). There was as little relationship between the intracellular and serum concentration of magnesium as there was for potassium.

Another important similarity between potassium and magnesium is the continued urinary excretion of magnesium even when the serum concentration of magnesium is reduced (Martin *et al.*, 1952). Conway (1956) believes that the behaviour of magnesium is influenced by the adrenal cortical hormones in a similar way to potassium Clinical disturbances due to magnesium deficiency are most likely to be encountered as part of the complex state associated with potassium depletion, but magnesium deficiency may itself cause renal tubular lesions (Greenberg *et al.*, 1938). Pure magnesium deficiency is probably very rare, but may occur when potassium depletion has been corrected solely by the administration of potassium salts and the consumption of food has not been resumed. Baldwin suggested that because of the close proportional association between potassium, magnesium and phosphate, it would be reasonable when trying to replace deficits of potassium to add magnesium and phosphate to the repair solutions This suggestion receives support from the observations of Flink *et al.* (1953), who found a serum magnesium concentration of 1 19 mEq per litre in a patient with severe potassium deficiency associated with alkalosis and phosphorus deficiency While this patient was receiving treatment for the potassium deficiency and alkalosis, she developed fibrillary twitchings, gross muscle tremors and choreiform movements of the linbs, jaw, tongue and facial muscles, and she was unable to eat or talk When magnesium sulphate was administered by intramuscular injection the twitchings promptly stopped and within 24 hours she was able to eat and talk Low serum magnesium concentration were subsequently found in 19 other patients suffering from delirium tremens of whom 15 improved after the intramuscular administration of magnesium sulphate Flink *et al* mention that magnesium deficiency causes "grass staggers" in horses and cattle; this can often be cured by the rapid intravenous injection of a solution containing magnesium

The normal daily requirement of magnesium during growth has been estimated at up to 10 mg per day, and since, like potassium ordinary foodstuffs contain an abundance of magnesium, in health magnesium deficiency must be very rare Balance studies in children have shown intakes of 200 to 300 mg per day, of which only 20 mg may be retained (Duckworth and Warnock, 1942) The magnesium content of cow's milk is 12 mg per 100 ml (12 per cent. of calcium content) and of human milk is 4 mg per 100 ml (10 per cent. of calcium content) According to Duckworth and Godden (1943) skeletal magnesium is very labile and is readily withdrawn from bone to replenish losses of magnesium from the soft tissues, the subsequent restoration of magnesium to the skeleton is much slower than its removal, perhaps because of the prior replacement of magnesium in the soft tissues Deficiency of magnesium disturbs calcium equilibrium, and it appears as if magnesium can replace calcium when this is deficient and magnesium is readily available. Miller (1944) has reported tetany which he ascribed to a deficiency of magnesium Levey *et al* (1956) showed that during the aspiration of upper gastro-intestinal secretions there is a close relationship between the volume of fluid removed and the loss of magnesium from the body, they have estimated that at least 100 mg magnesium should be administered each day if balance is to be maintained. Magnesium deficiency may be responsible for part of the clinical picture at present ascribed to potassium deficiency, and further improvement in the results of treatment of such disturbances may follow the administration of magnesium sulphate.

CHAPTER IV

THE MAINTENANCE OF CHEMICAL NEUTRALITY IN THE BODY

"ACID-BASE BALANCE"

NORMAL cellular function depends on the preservation of a suitable environment for the cells by the maintenance of a large enough volume of extracellular fluid at a suitable *p*H and concentration (or tonicity or osmotic pressure). This mainly depends in turn on the total quantity and concentration in the extracellular fluid of sodium and its principal associated anions, chloride and bicarbonate; normal cell function is also dependent on the maintenance of normal contents of calcium, magnesium and potassium within a narrow range of concentration in extracellular fluid. But the composition of extracellular fluid is subject to repeated disturbances by the addition of the products of digestion of food and of cellular metabolism, and by the removal of the components of the intestinal secretions, urine, insensible water loss and sweat. These various chemical surges of secretion, absorption and excretion, as well as the general tendency of the body by the accumulation of the products of metabolism to become more and more acid, are damped and resisted by various processes

The difficulty which many clinicians experience in understanding the processes involved in the regulation of chemical neutrality in the body is probably largely due to the terminology which is used. The loose and inconsistent use of the terms "acid" and "base" has caused clinical confusion, which is the greater because the meanings of these terms are so completely different to chemists and to doctors. The increasing use of the biochemical convention of milli-equivalents has made essential the revision of the chemical uses of the terms acid and base. The name "acid" was originally applied to substances which tasted sour and dissolved "bases" (alkalis, earths or metals) to form salts. Subsequently the theory of ionisation led to more precise definitions and the term acid was limited to a substance which could yield hydrogen ions and

a base was one which could produce hydroxyl ions Further modification led to the Bronsted Lowry proposition that an acid is a substance which yields hydrogen ions and a base, whereas a base is a substance which combines with hydrogen ions to form an acid. This is shown in Table XI, which also makes it clear

TABLE XI

Acid	⇌	Hydrogen ion	+ anion (base)
HA	⇌	H^+	+ A^-
HCl	⇌	H^+	+ Cl^-
a salt	⇌	a cation	+ an anion
NaCl	⇌	Na^+	+ Cl

that in this convention a base is usually an anion and that cations can combine with bases or anions to form acids or salts Moreover some substances such as ammonium ions which would not otherwise be thought of as acids can yield hydrogen ions and can therefore be considered as acids other substances such as the dihydrogen phosphate ion can like protein molecules, act as either acid or base according to the *p*H of the solution When these chemical terms are applied to the constituents of the body it is obvious that sodium and potassium ions are neither acids (since they cannot yield hydrogen ions) nor bases (since they cannot combine with hydrogen ions), and that they do not play any direct part in acid base regulation

The strongest acids are those which ionise most freely and therefore liberate more hydrogen ions. The anions of acids which are poorly ionised accept hydrogen ions more readily than do those of strong acids and therefore act more strongly as bases, *thus the strength of a base is inversely proportional to the readiness with which its corresponding acid is ionised.* Bicarbonate is a strong base, but chloride has almost no physiological activity as a base. Even a small amount of a strong acid will produce a large increase in the number of free hydrogen ions when added to a solution If the solution contains the salt of a weak acid such as sodium bicarbonate which is also ionised the bicarbonate accepts as many of the free hydrogen ions as it can, substituting for a highly dissociated strong free acid a much less dissociated weak acid. If a solution contains a weak acid and its salt, it can act in either direction and accept added hydrogen ions or basic ions, such a solution is known as a buffer In alkalosis the

hydrogen ion concentration decreases and *p*H rises, while in acidosis the hydrogen ion concentration is increased and *p*H falls.

The Buffer Systems of the Blood consist mainly of the sodium salts in the plasma and the potassium salts in the cells of carbonic acid, dihydrogen phosphoric acid and protein, in equilibrium with their corresponding acids. Acid-base balance in the body as a whole depends first on the immediate effects of these buffer systems on the body fluids. The buffer systems are of limited capacity and must be reinforced by the excretion of acid or base through the lungs or kidneys. The maintenance of *p*H within narrow limits thus depends primarily on the maintenance of suitable proportions of buffer acids to buffer bases, and the capacity of the buffer systems is clearly related to the quantities of buffer base or acid which are available. The mutual assistance which the buffering systems may provide is well illustrated by the amphoteric haemoglobin and oxyhaemoglobin. Their reversible combinations with carbon dioxide to form carbamino complexes differ because oxyhaemoglobin is a stronger acid than haemoglobin and can release more hydrogen ions. When therefore the breakdown of carbonic acid in the tissues tends to raise the concentration of hydrogen ions the conversion of oxyhaemoglobin to haemoglobin tends to reduce it. Moreover, haemoglobin has a much greater affinity for carbon dioxide than has oxyhaemoglobin.

The Bicarbonate-Carbon Dioxide System.—About a kilogram of carbon dioxide enters the capillary blood of a large adult each day. Some of this carbon dioxide dissolves in the plasma and forms carbonic acid which dissociates to liberate hydrogen and bicarbonate ions. About a quarter of the carbon dioxide combines, mainly with haemoglobin inside the red cell, to form carbamino-haemoglobin. The rest of the carbon dioxide is converted by the action of carbonic anhydrase in the red cell to carbonic acid which dissociates to hydrogen and bicarbonate ions. The hydrogen ions combine with haemoglobin, which prevents a change in *p*H (the isohydric shift). The bicarbonate ions diffuse out of the cell and their place is taken by chloride ions moving in (the chloride shift) In the lungs these changes are reversed when the equilibrium is disturbed by the loss of carbon dioxide from the blood as it passes through the pulmonary capillaries. The concentration of carbonic acid in extracellular fluid is related to

the carbon dioxide tension in the alveolar air, which in turn depends on respiratory exchange the plasma carbonic acid concentration is normally held at between 1 25 and 1 35 mEq per litre. The concentration of bicarbonate in extracellular fluid is controlled by the total quantity of cation, the "alkali reserve", which is available to combine with it This quantity of cation, which in the past was often called the total available base", is indicated by the amount by which the sum of the cations in extracellular fluid or plasma (sodium, potassium, magnesium and calcium) exceeds the sum of the anions (chloride phosphate, sulphate, keto acids and plasma proteins) This difference is equal to the quantity of carbonic acid which must enter into combination with cation to form bicarbonate in order to maintain the neutrality of reaction of the blood—the carbon dioxide combining power The normal amount of cation which is combined with bicarbonate is 25 to 27 mEq per litre The plasma carbonic acid and bicarbonate concentrations together determine the *p*H of the plasma under ordinary circumstances this is held with remarkable constancy at 7 4

Sodium is the most important extracellular cation, and when large quantities of it are lost by vomiting or diarrhoea, the reduction of total available cation disturbs the normal equilibrium between cations and anions Unless the accompanying loss of anion exactly balances that of cation and in the absence of rapid and accurate compensation, the loss of sodium leads to reduction in the alkali reserve and therefore of bicarbonate and a tendency to an alteration in extracellular *p*H An increase in anion content without a balancing rise in cation content also reduces the cation available to combine with bicarbonate and will lead to a compensatory reduction in bicarbonate and a tendency to a shift in *p*H

When acid is produced by metabolism or is absorbed from the intestine, it displaces bicarbonate from combination with cations in plasma or extracellular fluid, and carbonic acid is formed from which carbon dioxide is liberated and excreted in the lungs Conversely when acid is lost from the body its place in the chemical equilibrium with cations can be taken by bicarbonate, carbon dioxide being retained in the body to form the necessary carbonic acid The total quantity of anions which can be held in the body is dependent on the total quantity of cations present in

the body. The efficiency of the buffering of strong acids such as phosphoric, sulphuric or lactic by bicarbonate depends on the formation of a weak acid, carbonic, from which carbon dioxide is removed in the lungs. The most active cations, at least in the regulatory processes, are sodium and potassium, but much remains to be learned about the parts played by other ions and also by the sodium, and perhaps the calcium, in bone.

The Kidneys are probably the most important agents in the regulation of the composition of body fluid, since they are the chief means of conservation of sodium when this is deficient, and of excretion of acid when this is excessive. The kidneys are so efficient in chemical regulation that disturbances of *p*H seldom occur unless renal function is impaired Such alterations of *p*H are very rare in surgical patients and are usually due to marked reduction or increase in pulmonary ventilation, or severe disturbance of renal function.

The concentrations of sodium and bicarbonate in extracellular fluid are liable to disturbance by many factors. Sulphate and phosphate, produced by the oxidation of foodstuffs or by catabolism of body tissues, displace bicarbonate, combine with sodium and are filtered out in the glomeruli. On an ordinary mixed diet metabolism leads to the production of a urine of *p*H 5 0 to 6 0 and there is a diurnal rhythm of acid secretion which is related reciprocally to the output of sodium in the urine. If the renal tubules are unable to substitute another cation, such as ammonium, for the sodium and to recombine the latter with bicarbonate, sodium will be lost in the urine and extracellular fluid volume will fall. In one sense the kidneys may be regarded as the most important factors in chemical regulation, because they maintain in the extracellular fluid a stable concentration of cations 25 to 27 mEq. per litre in excess of the anions This reserve of cations is neutralised, as well as indicated, by the variable concentration of bicarbonate, and is readily available to combine with and neutralise any strong acid which is formed or introduced into the body.

The kidney may conserve sodium in three ways: first by reabsorbing the filtered sodium and bicarbonate from tubular urine; secondly by acidifying the urinary buffer salts; and thirdly by exchanging ammonium for the sodium combined with anions in the urine As Gilman and Brazeau (1953) have pointed

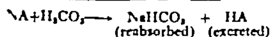
out, not only do these three processes have a common purpose the conservation of sodium and bicarbonate they also share the same mechanism of hydrogen ion sodium ion exchange in carrying out these varied functions.

It is not now credible that the differences between bladder urine and glomerular filtrate depend solely, or even largely, on modification of glomerular filtrate by selective reabsorption in the tubules, or even that all the eventual constituents of the urine are present

TABLE XII

Sodium and Hydrogen Ion Exchange

Tubular Urine	*Tubule Cell*	*Extracellular Fluid*
Na^+A^- ↓	$H\ OH^- + CO_2$ (carbonic anhydrase) ↓	
↓	H^+	
	HCO_3^-	
Na^+ →		
A^- ←	H^+	
↓	HCO_3^- ↓	
H^+A^-	$NaHCO_3$ — —	→ $NaHCO_3$



$$NA + H_2CO_3 \longrightarrow NaHCO_3\ (\text{reabsorbed}) + HA\ (\text{excreted})$$

Sodium-hydrogen ion exchange: the sodium ions in the tubular urine are exchanged with hydrogen ions from the carbonic acid formed in the tubule cell by action of carbonic anhydrase The free acid resulting from the transfer of hydrogen ions into the tubular urine is excreted and sodium is conserved.

in the glomerular filtrate. In 1945 Pitts and Alexander stated that since the quantity of acid in the urine might be far more than that contained in the glomerular filtrate hydrogen ion must have been added in the tubules They suggested that carbonic acid was formed in the tubular cells from carbon dioxide and water by the action of carbonic anhydrase (Tables XII and XIII) hydrogen ions from the carbonic acid contained in tubular cells were then exchanged with sodium ions in the tubular urine which thus became more acid The sodium, however, was conserved, passed into the extracellular fluid as sodium bicarbonate and reduced a tendency to acidosis They showed that when the activity of

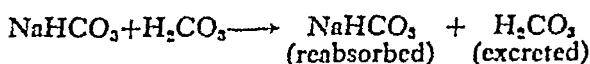
carbonic anhydrase was inhibited by sulphanilamide, the urinary acidity fell.

This complete reabsorption by the tubules of all the filtered sodium bicarbonate preserves sodium as well as preventing the development of acidosis Most of the sodium bicarbonate is absorbed in the proximal tubules and it used to be thought that the remainder was absorbed as sodium bicarbonate by the distal

TABLE XIII

Tubular Absorption of Sodium Bicarbonate

Tubular Urine	*Tubule Cell*	*Extracellular Fluid*
$NaHCO_3$ ↓	H^+OH^- + CO_2 (carbonic anhydrase) ↓	
Na^+ HCO_3^-	H^+ HCO_3^-	
Na^+ →	→	
←	← H^+	
HCO_3^-	HCO_3^- ↓	
H^+HCO_3 ↓	$NaHCO_3$ →	→ $NaHCO_3$



$$NaHCO_3 + H_2CO_3 \longrightarrow \underset{\text{(reabsorbed)}}{NaHCO_3} + \underset{\text{(excreted)}}{H_2CO_3}$$

tubules. However, Berliner (1952) has suggested that this distal absorption also may be due to sodium-hydrogen ion exchange. When tubular carbonic anhydrase was inhibited with Diamox, the urine became alkaline, and nearly half the filtered sodium bicarbonate was excreted in the urine The excretion of the sodium was due to inhibition of the sodium-hydrogen ion exchange, which depends on the promotion by carbonic anhydrase of the conversion of hydrogen and carbon dioxide to carbonic acid. They suggested that failure of reabsorption of bicarbonate was also due to inhibition of carbonic anhydrase Thus when the neutral salts of a weak buffer acid, such as disodium hydrogen phosphate, reach the renal tubules in glomerular filtrate, and react with carbonic acid formed in the tubular cells, sodium dihydrogen

phosphate and sodium bicarbonate are formed and the reabsorption of the latter promotes the progression of the reaction (Table XIV) Thus half the sodium combined with phosphate may be conserved and the reaction of the tubular urine becomes more acid The quantity of sodium which is thus conserved can be measured by the volume of 0 1 N alkali which must be added to the urine to return its pH to 7 4 (' titratable acidity")

TABLE XIV

Phosphate Excretion

Tubular Urine	*Tubule Cell*	*Extracellular Fluid*
Na_2HPO_4 ↓	$H\ OH + CO_2$ (carbonic anhydrase) ↓	
	$H\ HCO_3^-$	
Na^+ ——→		
Na^+ HPO_4^- ←——	H^+	
	HCO_3^- ↓	
NaH_2PO_4 ↓	$NaHCO_3$ ——→	$NaHCO_3$

$$Na_2HPO_4 + H_2CO_3 \longrightarrow \underset{\text{(excreted)}}{NaH_2PO_4} + \underset{\text{(reabsorbed)}}{NaHCO_3}$$

Each day about 173 litres of glomerular filtrate are formed containing (at 25 mEq per litre) 4500 mEq of bicarbonate, but only 1 to 2 mEq of bicarbonate may be excreted in the urine, the remainder having been repeatedly filtered and absorbed. At the maximum acidity which can be achieved, of pH 4 4, the urine is about a thousand times as acid as the extracellular fluid, this pH would be rapidly reached if the sodium in the tubular fluid were present only as salts of strong acids, for free strong acid would be formed by the sodium hydrogen ion exchange. The conservation of sodium and the continued excretion of strong acid does not depend solely on the presence and buffering action of phosphate, by the substitution of ammonium for sodium, strong acids are

and pH is indicated by the ratio between these components ($HCO_3 : H_2CO_3$). These two components may fluctuate over a wide range, but so long as they change proportionately pH is not altered. Only when the changes are disproportionate does pH rise or fall. Clinical disturbances of acid-base balance result when the various compensatory reactions to the loss or addition of acid or base can no longer maintain neutrality Such a disturbance may result from the loss of gastro-intestinal secretions containing cations such as sodium, potassium or hydrogen and anions like chloride and bicarbonate, and water, the ensuing compensatory reactions will involve the buffer systems, kidneys and lungs Although for ease of description simple "pure" types of disturbance are described and discussed, in nature the interactions between the many components are rapid and continuous and all that chemical analyses of plasma can do is to indicate part of the situation at the time the blood is withdrawn from the vein.

For clinical purposes acidosis and alkalosis are classified according to the predominant causal process into metabolic or respiratory types. The respiratory disturbances, by altering the rate of elimination of carbon dioxide, cause an increase or a decrease in the carbonic acid and hence the hydrogen ion concentration of extracellular fluid. In the metabolic disturbances there is an increase or a decrease in the bicarbonate ion concentration, which may be due to the loss of bicarbonate from the body in lost intestinal secretions, or may be a compensation for the loss or accumulation of an acid such as hydrochloric; the alteration in bicarbonate concentration disturbs the ratio of carbonic acid and bicarbonate and thus the pH.

Metabolic Acidosis.—In this, the common clinical type of acidosis, the rise in pH is caused by the reduction in the extracellular bicarbonate concentration. This may be due to the loss of bicarbonate in intestinal secretions by vomiting or diarrhoea, to the increased use of bicarbonate as a buffer against the increased production of keto acids in starvation or in diabetes, or of other organic acids in fever, infection or violent exercise, or may follow the administration of ammonium chloride. It may also be due to the diminished absorption of bicarbonate by the renal tubular cells or to the failure of the renal mechanisms for the transfer of hydrogen ions to the urine.

Clinical Features.—In surgical patients the loss of intestinal

secretions during prolonged diarrhoea, especially in the absence of vomiting, is probably the most important cause of this type of acidosis and this may be aggravated by the ketosis of starvation, especially in children The most marked clinical sign is the deep raucous and rapid respiration, the so-called 'air hunger", which is the main compensatory mechanism, the respiratory rate may rise to as fast as 50 per minute, but there are moments when the patient stops breathing and tries unsuccessfully to moisten his lips with a hard, brown, parched tongue. The respiratory centre is stimulated by the lowered pH, and by increased pulmonary exchange the plasma carbon dioxide concentration and also that of carbonic acid is reduced and the disturbed ratio between bicarbonate and carbonic acid tends to return towards normal When renal function is good, and is not impaired by the loss of fluid in the discharges from the body, an increase in ammonium excretion and if possible more complete sodium conservation will also help to reduce the acidosis and raise the pH

Diagnosis—A history may be obtained of the loss of intestinal secretions or of an operation such as transplantation of the ureters to the colon. Rarely the patient may be comatose when first seen, and this combined with stertorous respiration and what information can be obtained from relatives may be enough evidence on which to start treatment. Coma may be due to potassium depletion, or to the excessive loss of extracellular fluid (sodium and water depletion), and diabetic coma may also confuse the diagnosis and may be accompanied by changes in respiratory rhythm. The precise diagnosis of the degree of acidosis depends on the measurement of the plasma pH and concentrations of carbon dioxide and bicarbonate.

Treatment—This depends chiefly on reversing the causal disturbance as completely as possible and in assisting compensation as far as this can be done. Fortunately acidosis due to the loss of intestinal secretions is not only the commonest type found in surgical patients but also the one most susceptible to treatment the administration of Darrow's solution which contains sodium lactate and some potassium chloride, as well as sodium chloride, provides bicarbonate and potassium as well as the sodium and water which are the most important components of the lost secretions When there is a marked reduction of the extracellular fluid and plasma volumes, sufficient 0·9 per cent. saline should

nd *p*H is indicated by the ratio between these components HCO$_3$. H$_2$CO$_3$). These two components may fluctuate over a vide range, but so long as they change proportionately *p*H is not ltered. Only when the changes are disproportionate does *p*H ise or fall. Clinical disturbances of acid-base balance result when he various compensatory reactions to the loss or addition of acid r base can no longer maintain neutrality. Such a disturbance nay result from the loss of gastro-intestinal secretions containing ations such as sodium, potassium or hydrogen and anions like hloride and bicarbonate, and water, the ensuing compensatory eactions will involve the buffer systems, kidneys and lungs. lthough for ease of description simple "pure" types of disturb-nce are described and discussed, in nature the interactions etween the many components are rapid and continuous and all hat chemical analyses of plasma can do is to indicate part of the ituation at the time the blood is withdrawn from the vein.

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Diagnosis —A history may be obtained of the loss of intestinal secretions or of an operation such as transplantation of the ureters to the colon. Rarely the patient may be comatose when first seen, and this combined with stertorous respiration and what information can be obtained from relatives may be enough evidence on which to start treatment. Coma may be due to potassium depletion, or to the excessive loss of extracellular fluid (sodium and water depletion), and diabetic coma may also confuse the diagnosis and may be accompanied by changes in respiratory rhythm. The precise diagnosis of the degree of acidosis depends on the measurement of the plasma *p*H and concentrations of carbon dioxide and bicarbonate.

Treatment —This depends chiefly on reversing the causal disturbance as completely as possible and in assisting compensation as far as this can be done. Fortunately acidosis due to the loss of intestinal secretions is not only the commonest type found in surgical patients but also the one most susceptible to treatment, the administration of Darrow's solution which contains sodium lactate and some potassium chloride, as well as sodium chloride, provides bicarbonate and potassium as well as the sodium and water which are the most important components of the lost secretions When there is a marked reduction of the extracellular fluid and plasma volumes, sufficient 0·9 per cent. saline should

first be rapidly infused to restore extracellular fluid volume and an adequate circulation before any attempt is made to correct the accompanying acidosis. Acidosis due to renal failure does not respond well to the administration of sodium lactate, but remarkable improvement may follow dialysis of the blood in an "artificial kidney"; solutions containing potassium salts should never be used in the treatment of acidosis due to renal failure. Acidosis sometimes accompanies severe infections, but this type is seldom improved by the infusion of sodium lactate.

Respiratory Acidosis.—This is less common than the metabolic type and is normally caused by interference with gaseous exchange in the lungs leading to the retention of carbon dioxide. Poor pulmonary ventilation may be due to emphysema, pulmonary oedema or broncho-pneumonia especially when accompanied by cardiac failure. During anaesthesia, when muscle relaxants have paralysed the respiratory muscles, artificial ventilation may be inadequate, and in other types of closed-circuit anaesthesia the removal of carbon dioxide from the circulating gases may be inefficient, poliomyelitis also may reduce respiratory efficiency The respiratory centre may be depressed by brain injury or by poisoning with morphine, alcohol or the barbiturate drugs. In such circumstances compensation largely depends on the increased reabsorption in the renal tubules of sodium and bicarbonate and the increased renal excretion of hydrogen and ammonium ions.

Clinical Features—These depend on the cause and the degree to which compensation is effective During anaesthesia there may be a slow rise in systolic and diastolic blood pressures followed by a sharp fall when normal respiration is resumed and the retained carbon dioxide is eliminated. In most of the circumstances mentioned, respiration is abnormal and its correction is difficult

Treatment.—This depends on correction of the primary disturbance and in restoring normal respiratory exchange.

Metabolic Alkalosis.—In metabolic alkalosis the reduction in hydrogen ion concentration may be due either to the loss of hydrogen ions from the body (and thence a reduction in extracellular carbonic acid concentration) or to an absolute increase in the quantity and concentration of extracellular bicarbonate In surgical patients this type of disturbance is commonest when in pyloric stenosis the loss of acid by the repeated vomiting of gastric secretions is accentuated by the excessive consumption of sodium

bicarbonate, other antacids such as magnesium carbonate or trisilicate, bismuth carbonate or aluminium hydroxide also produce alkalosis. The chloride lost in the vomitus is replaced by retained bicarbonate, but it is important to remember that there are large losses also of potassium

Whereas the sodium and chloride contents of gastric juice decline when vomiting persists for a long time, the concentration of potassium is undiminished and in achlorhydria is increased because of the large amount of mucus with a high potassium content in the gastric juice. The combination of this continuing loss of potassium in the vomitus, with a daily loss in the urine which is increased by intracellular dehydration, and partial starvation due to the vomiting, results after several weeks in the loss of very large quantities of potassium Sodium is conserved efficiently by the kidneys, less is lost in the vomitus as the body content is reduced and reduction in extracellular fluid volume is now fairly readily recognised and treated by the rapid infusion of 0 9 per cent. saline. The insidious loss of potassium without replacement may lead to reductions of 1000 mEq or more, a third of the original body content. This is accompanied by severe extracellular alkalosis, but because, as Cooke *et al.* (1952) showed, two-thirds of the potassium lost from the cells is replaced by sodium ions and one third by hydrogen ions, there is an intracellular acidosis These changes in intracellular composition cannot be directly demonstrated in the patient in bed, whereas the extracellular alkalosis which is indicated by the carbon dioxide combining power can be readily measured. For this reason in the past the therapeutic emphasis has been placed mainly on replacement of sodium chloride and water and the correction of extra cellular alkalosis It has been recognised for a good many years that a small proportion of patients with prolonged vomiting due to pyloric stenosis and very severe extracellular alkalosis do not do well when treated in this way, their outlook improves when their large losses of potassium are assumed and are replaced. The only way in which the loss of potassium can be measured is by estimating the total exchangeable potassium content of the body, a procedure which is not widely available. Potassium depletion should be suspected whenever there is severe alkalosis

Alkalosis with potassium deficiency may be found also in some types of Cushing's disease, with some adrenal cortical neoplasms,

and after the prolonged administration of cortisone, ACTH or desoxycorticosterone acetate or the prolonged intravenous infusion of saline

To compensate for alkalosis there is a reduction in respiratory exchange, due to inhibition of the respiratory centre by the raised *p*H, leading to accumulation of carbon dioxide and thus of carbonic acid and a tendency to lowering of the *p*H. There is also an increase in the excretion of bicarbonate in the urine, which may be accompanied by an increase also in sodium excretion unless large amounts of sodium have been lost in the vomitus, and a reduction in the output of hydrogen ions, mainly by lowering of the ammonium and dihydrogen phosphate excretion.

Clinical Features.—The close association of severe alkalosis with other disturbances, especially potassium deficiency, makes it difficult to separate the typical features of the component factors of the combined disturbance. Mild degrees of alkalosis do not cause any particular clinical feature and can be recognised only by the raised plasma bicarbonate concentration. The most striking feature of severe alkalosis is the phasic respiration. A period of apnoea, varying in duration from 5 to 30 seconds or more, is followed by the onset of respiration which is at first shallow and then increases in depth until the excursion is normal; after two or three respirations of normal range the excursion again declines to apnoea. The number of breaths in each cycle varies from 5 to 10 or more and, with the variation in depth and the duration of the apnoeic periods, seems to be related to the severity of the chemical disturbance. The plasma bicarbonate concentration may be raised from the normal range of 23 4 to 32 5 mEq. per litre (52 to 72 volumes per 100 ml) to 36 to 54 mEq. per litre (80 to 120 volumes per 100 ml.). The blood urea nitrogen concentration is often, but not invariably, increased

Tetany may occur in severe alkalosis, but probably only during periods of altered *p*H of which tetany is therefore a good indication Tetany is due to an increased irritability of the skeletal muscles, irritability of muscle being inversely related to the concentration of free calcium ions in the extracellular fluid. The proportion of free calcium ions depends on the *p*H, and as *p*H rises calcium ions tend to combine with phosphate Hyperventilation may result in tetany, and it has been suggested that the cramp experienced by swimmers may be due to the hyperventilation

induced by cold water Tetany may also result from the administration of alkaline solutions of phosphate Latent tetany, in which the serum calcium concentration remains just above the level necessary for tetanic contraction to appear, may be more common than has previously been suspected. It can best be detected by compression by inflating a sphygmomanometer cuff round the arm, the hand then assumes a characteristic position of flexion at the metacarpo-phalangeal joints and wrists and extension of the interphalangeal joints (main d'accoucheur, Trousseau's sign) In animals, tetany indistinguishable from that due to calcium deficiency may be produced by feeding diets deficient in magnesium, the possibility that magnesium deficiency may be associated with severe alkalosis should not be overlooked.

Treatment.—In severe alkalosis due to vomiting in pyloric obstruction there are large losses of hydrogen, sodium and chloride ions and water the loss of potassium depends on the duration of the disturbance and the degree of starvation. While the first consideration is always to ensure survival by maintaining an adequate volume of blood in active circulation by restoring extracellular fluid volume, the effects of a large deficit of potassium on cellular function should not be ignored. Ammonium chloride has been advocated for the correction of alkalosis because this salt provides chloride with a cation, ammonium, which can be converted to urea in normal renal tubules and excreted, it has been said that ammonium chloride thus provides a specific means of correcting an alkalosis caused by loss of chloride. This recommendation ignores the loss of cations, especially of potassium, which is an important feature of alkalosis due to repeated vomiting, and the use of ammonium chloride does not provide the means of reversing the sodium transfer into cells or replace the loss of potassium from the body Ammonium chloride should not be used when alkalosis is associated with potassium deficiency The intravenous infusion of a solution of potassium chloride is necessary only in the initial stages and as soon as possible the oral administration should be started To replace 1000 mEq potassium very large quantities, such as supplements of 12 to 18 grams per day for three weeks or more, are needed in addition to an abundant intake of a good mixed diet, the daily administration of a few ounces of fruit juice of unknown quality and potassium content is of little use in a problem of this magnitude.

Respiratory Alkalosis.—In this type of alkalosis because of hyperventilation the tensions of carbon dioxide in the alveolar air and hence in the plasma are reduced and the extracellular carbonic acid concentration falls, the bicarbonate-carbonic acid relationship is disturbed and the *p*H rises. This probably occurs most commonly in surgical patients during anaesthesia because of excessive manual pulmonary ventilation in association with the use of muscle-relaxing agents. It may also occur in hyperventilation due to hysteria, at high altitudes, in men working in very hot dry atmospheres, in high fever and in salicylate or carbon monoxide poisoning. Compensation depends on the increased renal excretion of bicarbonate and is usually inadequate. During anaesthesia alkalosis is accompanied by pallor and a falling blood pressure. In both acidosis and alkalosis of respiratory origin there is some risk of respiratory arrest when the disturbance is severe, but this is much more common in alkalosis than in acidosis, possibly because over-ventilation is more common than too little ventilation which also produces cyanosis. Such alkalotic respiratory arrest can be corrected by the insufflation of carbon dioxide.

CHAPTER V

THE EFFECTS OF INJURY

SINCE ancient times wasting of the tissues and loss of body weight have been recognised as inevitable consequences of accidental or surgical injury, inflammation and fevers, and have been ascribed to such causes as toxaemia infection or the consumption of tissue by starvation In the natural wild state a severely injured animal, lacking its normal capacity for defence or flight, from new as well as old predators, must hide and be able to survive for several days without food or water If the animal does not die from loss of blood or infection survival during this period of starvation depends on the ability to provide from its own tissues not only the materials necessary for healing the injuries but also the continuing daily requirements of water and energy Both herbivorous and carnivorous animals survive and heal at the expense of large metabolic disturbances Man also possesses this inherent capacity to survive the combination of injury and starvation, but only a few observations seem to have been made on the biochemical basis of these post-traumatic phenomena before Cuthbertson (1930) described the well-marked alteration he had observed in the composition of the urine of patients suffering from fractures of the long bones. Since then many other investigations have shown how complex are the chemical and hormonic processes involved in the biological response to injury, and there is now wide but not unanimous agreement regarding the broad pattern of behaviour after severe injury is inflicted on a well nourished body An understanding of this normal reaction and also of how it may be affected by orthodox treatment is essential for the management of patients after many major operations, and it should not be forgotten that the inflammatory reaction is as old as life and that many patients recover in spite of much of the treatment they receive.

FLUID SHIFTS AFTER INJURY

Immediately after injury the development of the acute inflammatory response and the formation of an inflammatory

exudate cause the movement of fluid into the injured tissues and lead to a reduction in plasma and blood volume. Following this, there is a secondary shift of fluid out of normal tissues elsewhere in the body. Subsequently, as the inflammatory exudate resolves, there is a redistribution of fluid in the body (Fig. 4).

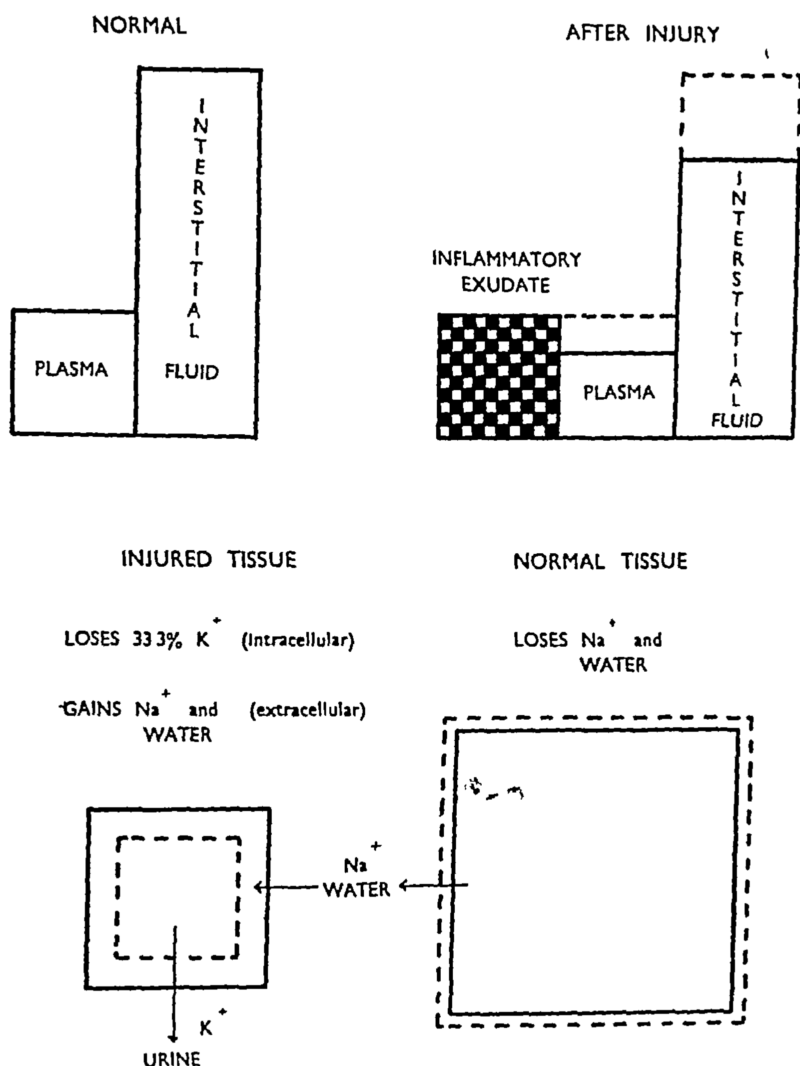


FIG 4—Fluid shifts after injury

(*a*) **Local Changes in Injured Tissues.**—After all injury, even in the absence of infection, an inflammatory exudate forms amongst the injured tissues This follows an alteration in capillary permeability which Lewis (1927) thought might be caused by substances which escaped from the damaged cells. The inflammatory exudate is rich in protein and resembles plasma, and in

thermal or chemical burns is the sole cause of the swelling of the injured part In lacerating or incised injuries there is also effusion of blood from divided blood vessels which contributes largely to the local swelling Blalock (1931) found in dogs that handling of the intestines, crushing of a hind limb or extensive burning caused a local loss of plasma like fluid, or of blood, equal to about 4 or 5 per cent of the body weight, or nearly half the total initial blood volume of the animal This work has since been repeatedly confirmed and indicates that the large shift of fluid out of the blood vessels into the extravascular space in the injured tissues reduces blood volume and may lead to circulatory failure It has also been shown by Fine and Seligman (1943) that the rate of lymph flow out of a burned limb may be increased up to eight times. At such a rapid rate of formation of lymph albumin crosses the capillary membrane in the damaged tissues as freely as sodium (Cope and Moore, 1944) and in the injured area the intravascular osmotic effect of albumin is lost. The rapid rate of lymph formation and outflow from the injured limb shows, however, that the inflammatory exudate undergoes constant turnover, although fluid accumulates in the swollen tissues, there is a very rapid flow of that fluid through the extravascular space from damaged capillaries to the lymph vessels. The swelling at the site of injury is due to the inflammatory exudate which is not static but is constantly changing its composition, and from this great flow of albuminous fluid through the injured tissues could be abstracted those substances which are needed for local repair Such an exudate is a dynamic local expansion of the extracellular fluid equivalent to as much as 4 or 5 per cent. of the body weight. It is initially derived from the blood plasma to which it is nearly equal in volume, and its provision is a first charge on the available extracellular fluid even at the expense of reducing plasma volume and circulatory efficiency Since not all such severely injured animals or human beings die of shock caused by blood or plasma loss even in the absence of treatment, there must be some means of compensating for the large local accumulation of fluid.

(*b*) **Changes in Uninjured Tissues.**—The amount of fluid which collected in the hind limbs of dogs crushed by a Blalock clamp was found by Ricca *et al* (1945) to be greater than could be accounted for by the measured loss of plasma. They further showed that the water and sodium content was increased in

damaged muscles but reduced in most of the uninjured parts of the body. Similar observations were made by Fox and Baer (1947) after scalding or the application of a tourniquet to the limbs of experimental animals; they also found that there was a marked loss of potassium from the cells of injured tissues. Rosenthal and Tabor (1945) found similar disturbances and calculated that after the application of a tourniquet the equivalent of all the sodium in the circulating plasma, or one-quarter of all the extracellular sodium, had accumulated in the injured area, which lost one-third of its original content of potassium. It seems clear that after injury there is a reduction in the volume of extracellular fluid (indicated by the sodium and water content) in the uninjured tissues. This is not associated with any abnormality in the capillaries of uninjured tissues, the permeability of which has been shown to be unimpaired (Fine and Seligman, 1943, 1944). In view of the compensatory shift of fluid out of undamaged tissues, the general condition and state of hydration are evidently important factors in determining the survival from severe injury.

As long as the rate of loss of fluid in the injured area exceeds that of withdrawal of fluid from intact tissues, plasma volume tends to fall. This leads to haemoconcentration in burns, but to haemodilution when the loss is largely of whole blood By releasing pressure bandages at various times after injury, Cameron *et al.* (1945) showed that the permeability of the capillaries does not return to normal for 3 to 5 days after injury, but long before this time the increased hydrostatic pressure in the swollen tissues has reduced the rate of loss of fluid from the capillaries. When normal capillary permeability is restored, most of the inflammatory exudate is usually rapidly reabsorbed

METABOLISM DURING RESTRICTION OF THE INTAKE OF WATER AND FOOD

It is customary for the consumption of food and water by most surgical patients to be restricted for 12 hours or more before, and for up to several days after, surgical operations The need for such restrictions varies with the site and nature of the operation, but they are commonly more lengthy and severe than is probably necessary. The effects of these restrictions are important and are superimposed on the disturbances in metabolism which are

directly the result of injury The wide differences of opinion which exist between surgeons regarding the need for the provision of parenteral supplies of water, glucose, sodium or potassium during the immediate post-operative period arise partly from a lack of sufficient information about the individual and combined effects of injury and restrictions of the intake of water and food Much of the early work in intravenous fluid therapy was done in North America, where the extremes of humidity and temperature which are inseparable from the continental type of climate may require, at certain seasons, higher intakes of sodium and water than are necessary in more temperate climates It seems necessary therefore to examine in some detail these aspects of human metabolism. The following description of what happens in normal uninjured subjects is derived from the work of Benedict (1915), Gamble (1947) and personal observations on volunteers in a temperate climate (Wilkinson *et al* 1949)

Deprivation of Water and Food.—When a healthy adult is deprived of both water and food the continuing oxidation of body protein and fat makes available about 200 to 300 ml of water per day, but the remaining 1300 ml of the theoretical minimal daily water requirement must be provided from water already in the body It is obtained from both extracellular and intracellular fluid. The quantities of sodium and potassium excreted in the urine indicate the degree to which the extracellular and intracellular fluids are used to provide the continuing daily requirements of water When the intake of both food and water is stopped, the loss of sodium and of extracellular fluid is greatest on the first day, declines during the next 3 days and is small from the fifth day onwards (Gamble, 1947)

The consumption of tissue protein is indicated by the quantity of nitrogen which is excreted in the urine, the nitrogen output usually falls on the first day of a fast, but then rises again during the next day or two before falling slowly but steadily as long as the fast continues (Benedict, 1915) On a normal diet the urinary output of potassium is related to the daily intake. When starvation begins, the urinary output of potassium usually falls to about 50 to 60 mEq per day and then very slowly declines throughout the fast. Part of this excreted potassium comes from catabolised protein, but some may follow the movement of water and potassium out of the cells, thus allowing the endogenous provision

of water for insensible water loss and the formation of urine. The volume of extracellular fluid is maintained by the renal conservation of sodium. Experiments in animals have shown that dehydration by thirsting leads to death when about 40 per cent. of the initial total body water has been lost, equivalent to about 17 litres in a 70-kg. man which at a steady rate of loss of 1300 ml. per day would be lost in about 13 days. This estimate has received support from observations on surgical patients dying of fluid losses of various kinds (Wilkinson, unpublished observations) In simple starvation, however, as the fast progresses there is a slow decline in metabolic rate, with a consequent reduction in the daily requirements of water for both insensible loss and urine formation, and survival is therefore possible for more than 13 days.

Deprivation of Food, Water being Supplied.—When ample water is provided for the fasting subject, the loss of body water is greatly reduced The continuing oxidation of protein and fat liberates 200 to 300 ml. of water. The renal conservation of sodium limits the loss of extracellular fluid, and the urinary output of sodium and potassium indicates that only about 500 ml. of body water are lost per day The remaining 800 ml. of the minimal requirement of 1500 ml. come from the water which is drunk. Gamble's subjects drank freely and in excess of their basal requirements of water, they excreted about 800 ml. of urine per day, which he therefore concluded was the minimum urine volume for fasting subjects under basal conditions. Observations on surgical patients under similar conditions agree closely with this figure

Deprivation of Food, Water and Glucose being Supplied.—The consumption of 100 g. glucose per day by an otherwise fasting adult prevents ketosis, which usually appears on the second day of the fast, and reduces the catabolism of body protein by about one-half The effect of the consumption of 500 calories and 2 5 litres of water per day on the urinary nitrogen excretion of an otherwise starving healthy volunteer is shown in Fig. 5. The reduction in protein catabolism is clearly indicated and the reduced nitrogen outputs of the two controls is in marked contrast with the rise in nitrogen output which follows operation. These alterations in endogenous metabolism also halve the quantity of solutes to be excreted by the kidney and therefore the minimum daily water requirements for urine formation No further benefit

results from the consumption of more than 100 g glucose per day, because this quantity reduces tissue protein catabolism to the

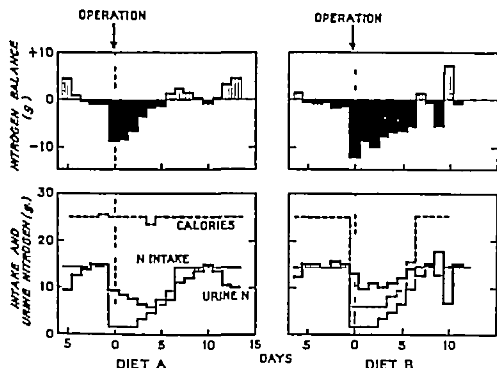


FIG. 5—This shows the effects of restrictions of diet on urinary nitrogen in normal volunteers not submitted to operation.

In diet A the intake of nitrogen was reduced but the intake of calories was maintained at 2,500 per day The intake of nitrogen is reduced from 14 4 g (90 g protein) to 1 6 g (10 g protein) on the day of imaginary operation and the two succeeding days (this small intake was designed to make the experiment less unpleasant for the volunteers) From the fourth day the nitrogen intake was increased as nearly as possible as it increases after partial gastrectomy

In diet B in addition to a similar restriction of protein intake, the daily intake of calories was reduced to 500 for three days (equivalent to the calories derived from 2·6 litres of 5 per cent. glucose solution) and then increased at a rate equal to that commonly achieved after partial gastrectomy

The results in one subject are shown The urinary excretion of nitrogen fell in both experiments but more markedly to 5-6 g per day near the minimum output possible when the calorie intake was maintained. When the calories were reduced the nitrogen output fell only to 8 10 g per day In both experiments the continued loss of nitrogen in the urine led to a negative nitrogen balance, indicating the destruction of tissue protein, but this was more severe when the intake of calories was reduced.

Reference to Fig 7 (p 96) will show that after an operation such as partial gastrectomy there is an increase in the urinary output of nitrogen (Wilkinson *et al.*, 1950 a).

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minimum of about 40 g per day The administration of glucose also reduces the loss of sodium in the urine by about half, but the potassium loss is reduced by only about one-sixth.

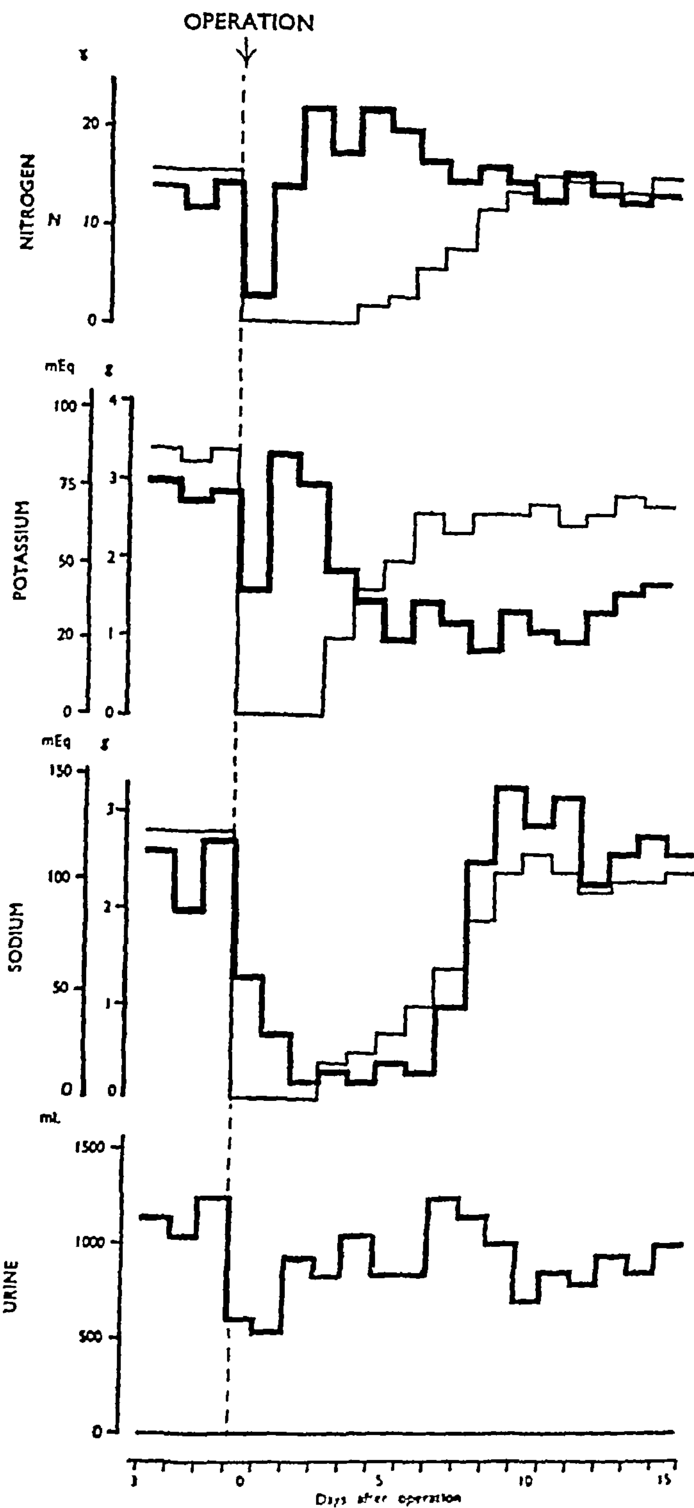


FIG 7—Urinary changes after partial gastrectomy Thick lines indicate ...inary output, thin lines indicate intake Afr... , there was a lar... nitrogen balance which lasted for 8 d... ...icated by the e... of nitrogen in the urine over the inta... negative po... lasted only 4 days after operation and ... a long period retention The negative sodium bal... ...d lasted for the urine contained little sodium ... the seven

after injury resemble the smallest volumes attainable by normal adults with good renal function (Gamble, 1954), and oliguria should be regarded as a normal response to severe injury combined with this type of starvation even when there has not been a severe loss of blood or plasma.

Although the volumes of urine passed by patients after operation and by normal volunteers subjected to similar restrictions of their intake of water and food are much the same, Dudley (1959) has pointed out that the osmolarity of the patient's urine may fall to only 500 to 700 mOs. per litre from the second day after operation This reduction in osmolarity as well as in volume is not unexpected, since it occurs when potassium diuresis has finished and sodium conservation is marked. It suggests that the oliguria after operation may depend on factors other than antidiuretic hormone, since the uncomplicated effect of this substance is to reduce volume and increase concentration and osmolarity

After injury the composition of the urine changes. The specific gravity rises almost immediately and, especially when water intake is restricted, remains high for a week or ten days Towards the end of the first day the quantity of nitrogen excreted in the urine increases greatly and continues to be abnormally high for six or more days, the peak being reached between the fourth and eighth days after accidental injury but rather earlier (between the second and fifth days) after various surgical operations (Cuthbertson,

TABLE XVI

Mobilisation of Potassium and Water from Muscle

Within 6 days of operation the excretion of 120 g nitrogen, in urine in excess of normal quantity if derived from body tissues, is equivalent to the catabolism of

(a) (N×6·25) 750 g protein
or (b) (N×30) 3600 g wet muscle.
containing up to 2850 ml. water
and 330 mEq potassium.

1936 Wilkinson *et al.*, 1950 a) (Fig 7) During the first ten days after a severe fracture or partial gastrectomy a well nourished adult patient may lose up to 120 g of nitrogen in the urine, if all this nitrogen is derived from skeletal muscle, it represents the catabolism of over 3 kg (6 6 lb) of tissue containing about 750 g of protein and nearly 3 litres of water (Table XVI) Cuthbertson found that the output of phosphorus and sulphur in the urine also

increased and that the proportions of them to nitrogen suggested that the excess output might be due to the catabolism of muscle.

The urinary excretion of potassium is usually markedly increased during the first 24 hours after injury (Howard *et al.*, 1946; Blixenkrone-Møller, 1949), from less than 50 mEq. per day before operation to 75 to 125 mEq per day, and this increase may last for 3 or 4 days The urinary output then usually falls below the daily pre-operative level and remains low for more than ten days. It was noticed later (Wilkinson *et al.*, 1950 b) that the excretions of potassium and phosphorus follow a parallel course and increase before those of nitrogen and sulphur. In 3 or 4 days, 4 to 8 g. (100 to 200 mEq) of potassium may be lost in the urine. This is equivalent to more than two or three times the total quantity of potassium in the extracellular fluid, and since the plasma potassium concentration does not appreciably change, the potassium excreted in the urine is derived from cells. The loss of 4 to 8 g of potassium represents the mobilisation of 750 to 1500 ml of water from the cells. The more rapid appearance of potassium than of nitrogen in the urine may be due to faster mobilisation of potassium, or to the slower catabolism of the nitrogenous part of the protoplasm.

Reduction in the urinary output of sodium from the pre-operative daily quantity of 100 mEq. or more begins soon after and sometimes even before operation, and may fall to as little as 25 mEq. or less from the third to fifth post-operative days. Towards the end of the first week after operation the sodium output rises and may exceed the pre-operative quantity during the second week. During this sodium conservation in the first week after operation, the *p*H of the urine is low These remarkable changes in renal function are shown in Fig 5, which illustrates the large increase in urinary potassium concentration at the same time as sodium excretion is much reduced.

In the absence of infection or persistent inflammation, the urinary output of nitrogen declines during the second week after operation or injury; about this time, provided a sufficiently liberal diet is being eaten, the intake of nitrogen should exceed its output or loss from the body. When recovery is uncomplicated, it is usual for such a positive balance of nitrogen, and of potassium, sulphur and phosphorus, to be achieved after about two weeks, and to persist for a varying time until much of the tissue catabolised during the first week after injury has been replaced

Although this evidence receives some additional support from the measurable alterations in the bulk of skeletal muscles after surgical operation, it is impossible to ascribe accurately the sources of nitrogen, potassium, sulphur and phosphorus which appear in the urine.

Cuthbertson (1936) showed that this post-traumatic tissue catabolism is not simply due to immobilisation or disuse atrophy, because although when a limb is fixed in a splint there are increased urinary outputs of sulphur, nitrogen, phosphorus, and later calcium, these increases last only a short time and are not nearly as large as after injury It has also been shown (Wilkinson *et al*, 1950 a) that while starvation undoubtedly accounts for some of the continuing urinary excretion of nitrogenous material after operation, the large increases in nitrogen, potassium, sulphur and phosphorus excretions are related mainly to the infliction of injury and their pattern of urinary excretion is different to that found during starvation

When the intake of water by all routes is maintained at about 4 litres per 24 hours LeQuesne and Lewis (1953) have shown that there is still invariably a period of oliguria after operations such as partial gastrectomy, this occurs even when 160 to 170 mEq of sodium or up to 200 mEq potassium per 24 hours is given in addition. In their patients the retention of water which accompanied the oliguria led to dilution of the extracellular fluid and also to a gain in weight. It is important to recognise that oliguria following deliberate or accidental injury may be just as intense in a patient who is loaded with water by intravenous infusion as it is in a patient who has been deprived of a water intake for 48 hours

It is generally agreed that stopping the intake of sodium results in a conservation of sodium by the kidneys the reabsorption of sodium from tubular urine being markedly increased. This process of sodium conservation is of gradual onset during simple starvation and takes 3 to 4 days to reach its maximum intensity After injury sodium conservation becomes more marked at an earlier stage and occurs regardless of the type of post-operative treatment which is provided, and, at least in the first 48 hours, is as intense in the patient to whom large quantities of sodium are administered by intravenous infusion as it is in those who receive none at all. Subsequently however, the effect of thus loading the body with sodium modifies to some extent, but does not entirely

obliterate, the normal pattern of post-operative sodium conservation which commonly lasts for up to a week after an operation such as partial gastrectomy. It seems likely, however, that the quantity of sodium which is excreted in the urine during the second week after operation bears a fairly close relationship to the quantity which has been administered during the first week after operation, that is to say, to the degree of sodium loading during the normal period of post-operative renal sodium conservation. It should be recognised that the reduction of sodium excretion by the kidney after injury is probably part of a very primitive device to preserve the volume of extracellular fluid, the immediate environment of the cells, which may not be much affected by such biologically recent innovations as the continuous intravenous infusion.

Blixenkrone-Møller (1949) thought that the post-operative urinary excretion of potassium was smaller when adequate volumes of fluid were administered during the first few days after operation than when the intake of fluid was restricted. This has not been confirmed in recent observations (Wilkinson, 1956 b), from which it appears that there is little difference in the post-operative urinary excretion of potassium, no matter how much or how little water is administered.

In the presence of infection, of complications such as thrombophlebitis, or of extensive areas of granulation tissue, renal sodium retention and the destruction of protein tissue continue, and the latter leads to further loss of body weight.

The initial period of 6 to 8 days after injury, which appeared to be characterised by the destruction of protein tissue, Cuthbertson called the "catabolic phase". He further suggested that this destruction of protein tissue might be a means of supplying energy or amino acids, or both, for the purposes of repair of the injury, perhaps the survival of a primitive response in the starving animal unable to obtain food.

It is important to recognise that all the protein in the body takes some part in this response. The dynamic equilibrium between individual protein components, and between these peptides and amino acids and carbohydrate and fat, first described by Schoenheimer (1942), indicates the folly of trying to consider protein economy in isolation from the other potential sources of energy and cellular components. The quantitative relationships which can be established after operation or other injury, between the

urinary output of nitrogen and the decline in total circulating plasma albumin and the destruction of red blood corpuscles in the so-called ' anaemia of trauma ', are further indications of the close relationships and mutual equilibria between the individual items of the total protein mass of the body Moreover, this "catabolic response" is not confined to man and the other mammals, but is clearly exhibited also by the shore-crab Carcinus and earthworms (Needham, 1955, 1958)

Both the quantity of protein tissue catabolised and the excess nitrogen output in the urine are related to the state of protein nutrition of the body at the time it is injured and to the severity of the injury Previously well nourished patients produce a maximum catabolic response if the injury is sufficiently severe and the intensity of the response is related to severity of injury (Moore and Ball, 1952), but patients who have suffered from malnutrition and who are already deficient in protein at the time of injury produce a proportionately less marked catabolic response, when malnutrition is severe, there may be little or no increase in urinary nitrogen excretion after injury In such wasted patients breakdown of operation wounds is more common and healing is slower, and there is some evidence that these features can be related to impaired maturation of the fibroblasts in the healing tissues (Kobak *et al*, 1947) however the possibility that an associated vitamin C deficiency may also be concerned in this disturbance should not be forgotten. This impairment of healing in the previously malnourished subject is in sharp contrast to the normal healing, in spite of starvation after injury, which is exhibited by well nourished patients.

After severe injury appetite is commonly lost for 3 or 4 days and the emptying of the stomach is delayed, the gastric phase of digestion is slowed and food eaten shortly before injury may be vomited unchanged 24 hours later The futility of drinking water as a means or relieving thirst after major operations and the frequency with which this is followed by vomiting are also well known. Scholer and Code (1954) showed that even in normal subjects the rate of absorption of heavy water from the small intestine was 10 times as fast as from the stomach, by combining the heavy water with a barium suspension they showed that this difference was due to the rapid distribution of the water in a thin film over a large mucosal surface in the small intestine, whereas it

lay in one place in a puddle in the stomach. Howard (1955) showed that the normal delay in gastric absorption of water was even greater after injury, and in later studies (Drawhorn and Howard, 1957) found that intra-abdominal injuries had a more marked effect than burns or other injuries of the chest or limbs, and that partial gastrectomy produced the most prolonged disturbance.

It is now evident that the protein catabolism is only one feature of a general response by the body to injury which appears to consist of two phases. In the one, retention of sodium and chloride as the result of efficient conservation by the kidneys is accompanied by the maintenance of volume and composition of the extracellular fluid In addition, there is a transfer of extracellular fluid from the interstitial space in the uninjured tissues to the damaged tissues. In the other, cellular destruction results in the loss in the urine of such constituents of protoplasm as nitrogen, potassium, phosphorus and sulphur, and in the absence of intake, the water from the catabolised protoplasm is presumably available for insensible water loss and urine formation.

From about 10 to 14 days after injury the body enters the "anabolic phase", which may last for several weeks. This is the period of reconstruction following healing of the wound when the previously catabolised normal tissues are replaced. The duration of the anabolic period depends on the severity of the injury and the intensity of the catabolic tissue destruction, and also on the provision in the diet of sufficient energy and protein to allow for the formation of new tissue in addition to the ordinary daily requirements.

ENERGY REQUIREMENTS

Little is known about the energy requirements of injured people, but Cuthbertson (1945) has suggested that the normal daily minimum is probably 2100 calories for a 70-kg. man (30 calories per kg.) and that after injury much more is required. Cuthbertson (1936) found that during the first 12 days after severe compound fractures or surgical operations the respiratory quotient varied from 0·76 to 0·85, thereafter it gradually rose to 1·15. This indicates that during the first 12 days his patients were deriving 50 to 80 per cent. of their total calorie requirements from fat and

that later they passed into an intensely anabolic phase while fat and other tissues were being restored For comparison it may be noted that the hibernating marmot has a respiratory quotient of 0 7 and that during the fattening of farm animals the respiratory quotient may rise as high as 1 4 (Best and Taylor, 1955) Cuthbertson also noticed that oxygen consumption rose as the urinary nitrogen excretion rose, but fell from the fourth day onwards although the urinary nitrogen excretion remained large, about this time the consumption of food had been resumed and was again providing a proportion of the energy requirements Cuthbertson (1957) after re-examining his earlier (1932) data concluded that during the first week after injury the energy liberated by the oxidation of protein could alone account for the rise in basal oxygen consumption which he had earlier observed, and that there is no indication of any post traumatic increase in the oxidation of fat and carbohydrate. In rats, heat production does not rise after injury if the animals are not fed protein nor does the urinary nitrogen excretion of adrenalectomised rats increase after further injury unless they are maintained on a sufficiently large dose of cortisone.

Even at the height of the catabolic period, when 20 to 30 g of nitrogen may be excreted daily in the urine, the calories derived from protein, assuming that its metabolism is complete, would amount to only 500 to 750 per day There is no reason to suspect that the daily energy requirements are reduced after injury, indeed, everything points to an increase and the remaining 1800 to 2000 calories out of a total energy expenditure of 2500 to 3000 in 24 hours must be assumed to come largely if not entirely from the fat stores. this would require the oxidation of more than 200 g fat per day Although this estimate appears high, Keys *et al.* (1950) found that in partial starvation without injury 5 27 kg of fat were lost in 12 weeks, an average of 63 g per day, which if completely metabolised would yield 567 calories From the examination of a very large number of published and personal metabolic studies it is evident that during the second week after injury in the absence of secondary inflammation a daily intake of at least 1800 calories and about 11 g of nitrogen is essential before protein equilibrium (nitrogen balance) can be achieved.

The possible effects of the catabolism of body tissue after injury are shown in Table XVII The excretion during 24 hours of

20 g. nitrogen in the urine is assumed to indicate the consumption of 600 g. of whole tissue, such as muscle, with the release of 475 ml. of tissue water, 55 ml. water of oxidation and 500 calories; about 50 to 60 mEq. (1 9 to 2 3 g.) potassium also are released. If in addition 250 g fat are burned, then this provides up to 267 ml. water, making a total of about 800 ml. The total daily water requirements of a 70-kg. man also are shown in Table XVII,

TABLE XVII

Calories and Water derived from Catabolism of Fat and Protein after Operation

Calories

20 g urinary nitrogen = (N × 30) 600 g whole muscle
or (N × 6 25) 125 g protein
= 500 calories

At R Q of 0 76, 80% of total calories are derived from fat

If total calorie consumption is 2500 calories, 2000 calories are derived from fat requiring oxidation of 250 g. fat.

Water derived from tissue oxidation

600 g muscle provide	475 ml	tissue water
	55 ml	water of oxidation
250 g. fat provide	267 5 ml	water of oxidation
	797 5 ml.	

Water requirements for consumption of 2500 calories

Insensible water loss dissipates 25% of total heat production
= 625 calories

625 calories will evaporate $\frac{625}{0\ 58}$ g. water
= 1077 ml = insensible water loss.

Minimum urinary water = 500 ml

Therefore minimum total water requirements = 1577 ml./day, of which 797 5 can be provided by tissue catabolism

Therefore a minimum of 700 to 800 ml water should be supplied each day.

comprising at least 1077 ml. for insensible water loss and 500 ml. for urine There is a difference of at least 700 ml. between the most that is likely to be provided from the tissues of the body and the basal water requirements, this water is at present assumed to come from the extracellular and intracellular fluids. It is probably only this fraction of the water requirements which can be affected by the supply of water from outside the body, since the water derived from the catabolism of body tissues will be made available regardless of the quantity of water supplied

BODY WEIGHT CHANGES

The loss of weight which invariably follows severe injury to a well nourished person may amount to 10 per cent or more of the initial body weight. The time of onset of this weight loss depends mainly on the way in which the patient is treated after operation The most "natural' response is seen in the patient who for 48 hours after operation is not given any food or fluid by mouth or parenterally, but thereafter is given small quantities of water for 2 days and subsequently is allowed to resume gradually the consumption of a normal diet (Wilkinson, 1956 b) In such a patient weight loss begins during the operation and continues at a rapid rate for 48 to 72 hours, up to 10 per cent. or even more of the initial weight being lost, this period of rapid weight loss is followed by one in which there is little change and then weight rises again (Fig 8) When unoperated control subjects are treated in the same way, the pattern of weight change is similar, but the average weight loss is smaller in the controls than after operation and the subsequent recovery of weight is more complete A similar patient whose oral intake is stopped, but who receives parenteral fluid during the first three or four days after operation and then is gradually fed, loses less weight during the first four days, but the weight loss continues for a longer time and is as great after fourteen days as in the patient who did not receive parenteral fluid The post-operative loss of weight is due to the summation of several factors. The catabolism of tissue, the insensible and urinary loss of body water and the aspiration of gastric secretions cause the rapid loss seen in the patient who does not receive any parenteral fluid. When saline is administered by the rectal or intravenous route, most of the sodium it contains is retained along with water by the conserving action of the kidneys, and this offsets the normal weight reduction Similarly because after injury the kidneys deal less effectively with large water loads, the infusion of large quantities of glucose solution leads to temporary retention of a variable proportion of the water, which increases body weight. Only after about the sixth day when the kidneys cease to retain sodium are the administered sodium and water excreted and does body weight fall to its true level. It has been repeatedly observed that patients who do not receive parenteral fluids after partial gastrectomy recover their appetite more rapidly and eat more

food sooner than patients who are given saline or glucose solution by rectal or intravenous infusion. When drinking is stopped completely for 48 hours after partial gastrectomy, less fluid is lost by gastric aspiration than when limited or free drinking is allowed.

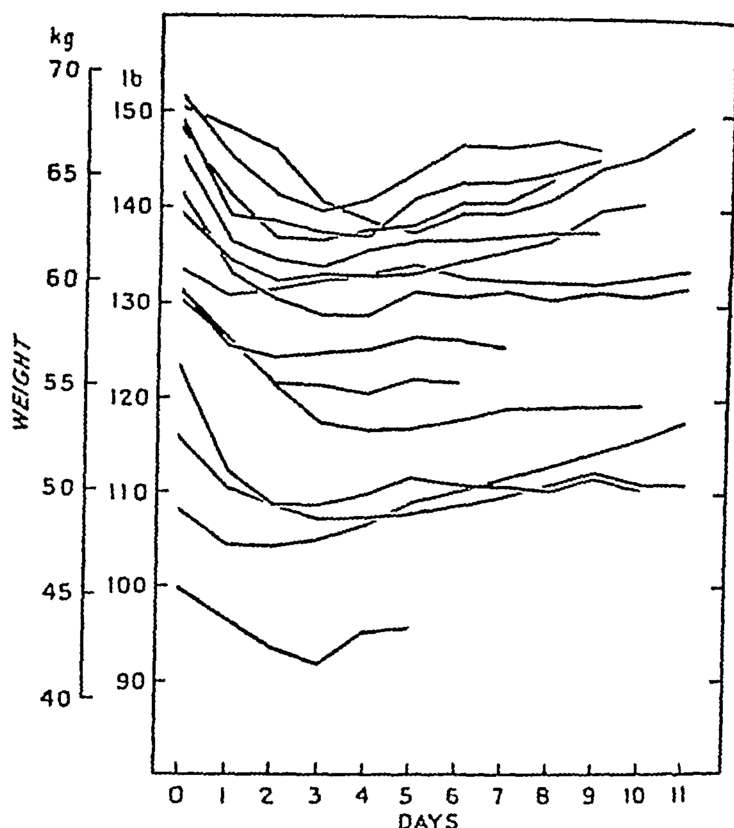


FIG 8—Weight changes in patients submitted to stoppage of water intake for two days and of food intake for four days after partial gastrectomy, showing the rapid and large initial loss of weight associated with complete water lack, and the subsequent gain in weight (Wilkinson, 1956 b)
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It follows, too, that reduction of urinary volume does not necessarily indicate the retention of water in the body. When fluid restriction is complete for 48 hours after operation, the urine volume remains small (500 to 800 ml.) for 48 to 72 hours, but there is then usually an increase to 1000 or more per 24 hours for a day or two, although the oral intake may be less than sufficient to account for this increase. This basic pattern is not much disturbed by the administration of fluid by oral, rectal or intravenous routes or by the composition of the administered fluid unless the volumes are excessive.

CHEMICAL CHANGES IN BLOOD

After injury the composition of the blood remains remarkably constant in spite of the large shifts of body fluid and great catabolism and alteration of body tissues The chemical changes in the blood which may occur depend a good deal on the quantity and type of fluid which may be administered, especially by the intravenous route When the administration of fluid is restricted, the most marked change is a rise in the packed cell volume, developing during the first 2 or 3 days, and then gradually falling over the next 5 or 6 days below the initial value, and slowly rising again towards its original level after 10 to 14 days. This change in packed cell volume is accompanied by a reduction in total plasma protein concentration due mainly to a reduction of the concentration of the albumin fraction, which usually persists for several weeks The globulin concentration may fall for only a day or two and thereafter is usually above its initial level until the albumin concentration returns to normal Other changes in the blood chemistry are inconstant. When the fluid intake is restricted the serum sodium concentration like the packed cell volume usually rises for a few days. The urea concentration also often rises slowly for a day or two after operation, but there are no regular alterations in the composition of the blood except those in packed cell volume and plasma protein concentration. When fluid is administered, the subsequent changes are closely related to the composition of the fluid given, and the volume and the rate at which it is injected. The serum sodium concentration tends to be maintained by the intravenous infusion of isotonic saline, but when glucose solution is infused, there is often a subsequent decline in the serum sodium concentration

Much attention has been given to the fall in serum sodium concentration which may follow soon after operation despite the close renal conservation of sodium the absence of extrarenal loss of sodium, and an increasing total body sodium content, the so-called 'sodium paradox This reduction in serum sodium concentration is undoubtedly common in association with intra venous therapy and may be due to the retention of water, which being distributed mainly in the extracellular fluid leads to dilution of the extracellular sodium The weight of patients who exhibit sodium dilution soon after operation seldom changes much and

important respects. Although the effects vary with changes in dosage, either ACTH or cortisone will cause increases in the urinary excretion of nitrogen, potassium, calcium and phosphorus and the retention of sodium, chloride and water. Ingle *et al.* (1947) reported that such effects of cortisone diminish after about ten days, as if this substance lost its effect or the body had become refractory to it; this observation is of interest because after injury the catabolism of body tissue may be prolonged by infective complications and the change from catabolism to anabolism occurs only when infection is overcome. Campbell *et al* (1954) found that in rats the increase in urinary nitrogen was similar after the implantation of 25 mg. cortisone acetate to that produced by fracture of the shaft of the femur. When adrenalectomised animals are maintained on saline alone they do not produce the characteristic alteration in urinary nitrogen excretion after fracture of the femur, but when they are maintained on a sufficiently large dose of cortisone the urinary nitrogen excretion rises normally after fracture of the femur. It is evident that a normal response to injury can occur in the absence of the adrenal glands provided there is an adequate quantity of adrenal extract or cortisone in the body, and an abundance of clinical experience has shown that this applies also to men and women after ablation of their adrenal or pituitary glands. When after bilateral adrenalectomy the patient is maintained with adequate doses of cortisone there are still increases in the urinary output of potassium and nitrogen and a reduction in sodium excretion in the pattern characteristic of patients with intact adrenal glands, the dose of cortisone need not be increased to enable the patient to recover from the removal of the second gland provided enough cortisone is already being given (Robson *et al.*, 1956; Wilkinson, 1956 a). The production of aldosterone ceases after adrenalectomy, but provided the dose of cortisone is adequate, a normal pattern of change in renal function develops.

It has been concluded from these observations that an increased adrenal steroid output is not essential for the production of the normal response to injury (Engel, 1951; Ingle, 1952) but that some factor other than the adrenal hormones is the primary agent after injury, although the full development of the response depends on sufficient adrenal hormones being present. *Cortisone* combines powerful actions, both on mineral metabolism leading to

sodium retention and on protein and carbohydrate metabolism and perhaps for this reason is a more effective substitute for the adrenal glands than agents which have a poor mineral effect such as prednisone or a mild effect on protein, but a much more intense mineral activity, such as aldosterone, neither of these substances can maintain stability after total adrenalectomy

There has been considerable discussion of the ways in which the adrenal hormones may produce their effects after injury Ingle (1951) suggested that the hormones "permitted' the action of some unknown stimulus resulting from injury on a tissue or organ, this idea implies that the hormone renders a cell responsive to a stimulus and that if there is insufficient hormone circulating in the body the stimulus will not be effective Albright (1942) suggested that the glucocorticoids might have an anti anabolic rather than a catabolic action on protein, that their action might be to inhibit the formation of new protein rather than simply the destruction of tissue already existing This idea was taken further by White and Roberts (1950) and by Roberts (1951 1952), whose work suggests that the mobilisation of tissue protein is an important effect of adrenal cortical hormones. Recently Roberts (1953) has shown that the mobilisation and transfer of tissue protein, under the influence of these hormones, may in one place represent anabolism and at the same time in a different situation in the same body be catabolism This is particularly applicable to the injured animal, in which the protein from undamaged tissues is transferred to injured structures. Some years ago Fischer (1947) suggested that for such transfers the plasma albumin offered a convenient and ubiquitous vehicle, the scope of which is increased by the altered capillary permeability of acute inflammation.

If the action of a hormone is related to its concentration in extracellular fluid it might be expected that the measurement of change in blood concentration would give a better idea of the effects of injury than estimation of the urinary excretion of largely inactive conjugated residues After abdominal operation, Steenburg *et al* (1956) found the free serum 17-hydroxycorticoid concentration rose steeply, reached a peak within a few hours, and then declined to a normal concentration within 48 hours but there was no relationship between serum concentration and the urinary excretion of corticoid substances. The rise in serum corticoid concentration coincided with the usual post-operative increase in

urinary output of potassium and the fall in circulating eosinophils, preceded the rise in urinary nitrogen excretion, and was unrelated to the onset of sodium conservation. Samuels and his colleagues (Sandberg *et al*, 1954; Eik-Nes *et al*, 1955) reported similar changes in serum concentrations of corticoids and have emphasised the importance of altered liver function in determining the rate of removal of natural or infused 17-hydroxycorticoid and thus of the serum concentration.

When a dog or man is cooled, amongst many other functional changes, there are reductions in adrenal blood flow and the output of 17-hydroxycorticoids, but both return to normal on rewarming (Bernhard and McMurrey, 1955; Bernhard *et al.*, 1956). During cooling, in spite of the reduced output by the adrenal, the blood corticoid concentration rose whether the liver was excluded from the circulation or not. The altered blood corticoid concentration did not change on the infliction of injury or the injection of ACTH The marked reduction in output thus is more than counterbalanced by the reduced rate of conjugation in the liver, oxidation in the tissues or excretion in the urine Hypothermic patients exhibit a small rise of serum corticoids when anaesthesia is induced, but not the later marked increase which is the typical response to injury at normal temperature; even when the body temperature rose after the procedure the serum concentration did not rise to a normal degree Cooled patients produce a normal response to injury as judged by the alterations in urinary composition and body weight, in spite of apparently marked modification of the output of the corticoid hormones on which the response is believed to depend Much remains uncertain, but it seems likely that although cooling affects all bodily function to some degree, production of the hormone is less disturbed than conjugation, excretion or utilisation, and the necessary excess is provided.

In 1950 Deming and Luetscher described a sodium-retaining corticoid which later was found to be identical with aldosterone (18-aldocorticosterone) which Simpson *et al.* (1954) isolated from beef adrenals. The concentration of aldosterone in blood and its output in the urine are very small compared with other adrenal cortical hormones. It has little effect on carbohydrate or protein metabolism (Prunty *et al.*, 1955), but has about thirty times as powerful an activity on sodium and potassium metabolism as desoxycorticosterone; both hormones are similar in causing a

rapid increase in urinary potassium output and a rather slower onset of sodium conservation After injury the urinary output of aldosterone rises promptly but there is wide individual variation both in pre-operative daily output and the size of the increase after injury It has been suggested that the post-operative increased output of aldosterone is a response to the starvation with consequent restriction of sodium intake which accompanies injury, this does not accord well with the delay in onset of sodium conservation shown by some patients or its onset 24 hours before operation in other people moreover the urinary output of sodium falls even when the sodium intake is maintained through the post-operative period, and in these circumstances the greater part of the administered sodium is retained in the body Bartter (1956) has shown that the output of aldosterone is independent of extracellular sodium concentration or the total body content of sodium, but is related to change in the volume of extracellular fluid and especially of plasma volume. The output of aldosterone is raised in patients with oedema in hepatic cirrhosis nephrosis or cardiac failure, in eclampsia and pregnancy and in primary aldosteronism due to tumour or to bilateral adrenal hyperplasia.

While it seems certain that survival from a severe inflammatory reaction whether it is due to injury or infection, depends on satisfactory adrenal function or adequate substitution therapy, the precise part played by the various adrenal cortical hormones remains rather obscure. Little is known of the primary factors which initiate the hormonal response to injury or of the way in which these hormones may produce such of their effects which are known. Some of those who have been able to reduce the urinary output of potassium or nitrogen, by preventing or diminishing the effects of starvation after operation by the intravenous administration of fat emulsions and solutions of amino acids, believe that their success in altering the post-operative metabolic pattern implies that the adrenal cortical hormones exert only a limited influence on the metabolic changes after injury Once more it must be emphasised that if animals in the natural wild state are to avoid death, they must be able to survive starvation for water and food, as well as to heal their wounds and resist infection, and that the means of doing all these things must be found in their own bodies. That the intravenous provision of energy and foreign amino acids appears to modify the biological

response to injury may mean merely that part of the normal process to provide all the continuing daily requirements of energy and protein is no longer necessary.

Some of the sequels to injury may occasionally resemble the effects of the administration of large doses of adrenal hormones. Prolonged reduction in the rate of disposal of normal hormones secreted in a normal response to severe injury may lead to persistent high circulating concentrations of these hormones. Prolonged elevation of the blood corticoid concentrations has been found after burns and other severe injuries, without any anatomical evidence of abnormality of the adrenal glands (Hume and Nelson, 1954) These high circulating concentrations of adrenal corticoids may be connected with the production of Curling's ulcer, of such vascular changes as necrotising arteritis or focal bleeding, and of poor healing responses (Dudley, 1959).

THERAPEUTIC IMPLICATIONS

It is obviously important to decide from our present knowledge of the effects of injury whether the normal response of the body can be modified beneficially in any way. The catabolism of protein tissue, the loss of potassium and nitrogen in the urine and the retention of sodium and water during the first week are brought about, at least in part, by the action of adrenal cortical hormones; the production of these hormones depends in turn on the influence of the pituitary and possibly of centres in the hypothalamus or elsewhere. Any alteration in the components of the whole reaction to injury must depend on alteration of the hormonic control of the reaction, particularly of the unknown initiating factors (Fig. 9).

The catabolism of protein tissue after injury can be somewhat reduced by the prevention or mitigation of accompanying starvation, but the degree to which this is feasible in a surgical patient depends on appetite and the ability to consume food. Appetite is usually poor or absent for several days after a major operation and the patient may have little inclination to eat even if the post-operative state of his gastro-intestinal tract permits the consumption of food. The delay in the absorption of water after severe injury, which may last for 48 hours or more even when the stomach

and intestines are uninjured, has already been mentioned. Attempts to maintain an undiminished intake of calories and protein throughout the post-operative period by the intravenous infusion of fat emulsions and solutions of amino acids are expensive and cause appreciable extra discomfort to the patient, such supplements seldom provide adequate quantities of potassium, phosphate

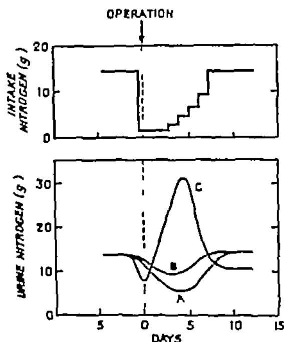


FIG. 9—Smoothed curves of the urinary nitrogen excretions in a volunteer control subject submitted to dietary restrictions but not to operation (A and B as in Fig 5 p 93) and in a man who was submitted to partial gastrectomy In each kind of starvation the urinary nitrogen excretion fell at a stage when after operation combined with starvation there was a marked rise. The initial fall in output after operation was related to the small volume of urine which was passed on the day of operation. It was concluded that the difference between the lower two curves was related to the amount of tissue protein spared by the maintenance of the calorie intake in diet A, while the difference between the upper two curves reflects the protein catabolism resulting from partial gastrectomy in a well nourished adult man (Wilkinson *et al.*, 1950 a)
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or sulphate which are probably also necessary if protein tissue is to be spared or re-formed There is no evidence that supplements of protein components can be used in preference to endogenous protein during the so-called catabolic phase, it is reasonable to expect that, starvation apart, whatever fraction of such destruction of protein tissue is due to the hormonal changes induced by injury will persist in spite of the administration of exogenous amino

acids so long as the normal pattern of hormone secretion is not altered (Fig. 10).

The urinary loss of potassium immediately after injury has led some workers to advocate the administration of potassium salts at

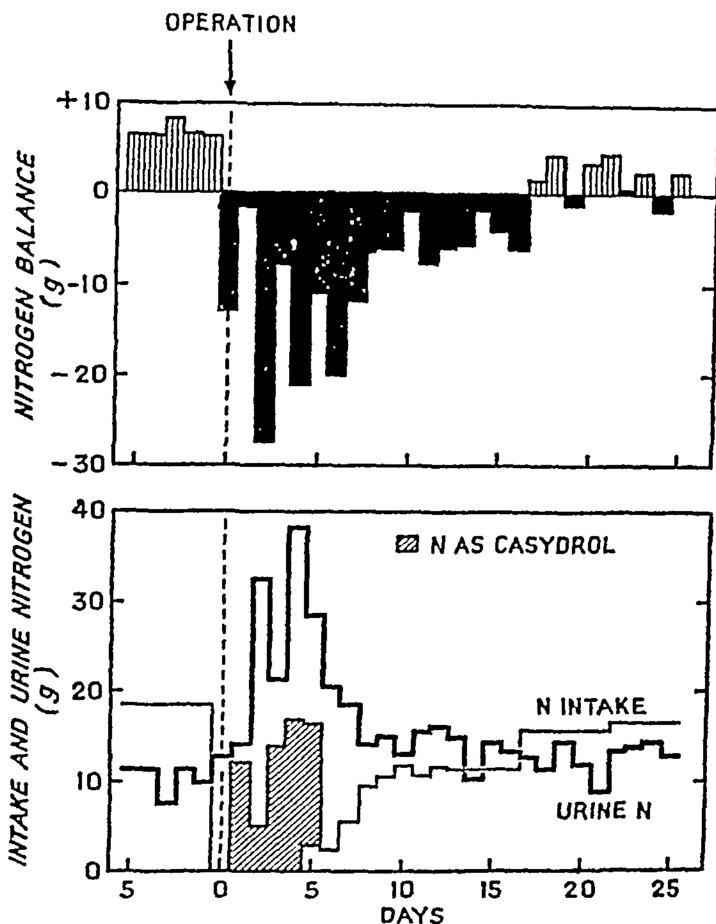


FIG 10.—Nitrogen balance, intake and output before and after partial gastrectomy for duodenal ulcer in a well nourished man to whom protein hydrolysate was given by intravenous infusion for five days after operation The intake of non-protein calories was insufficient and the equivalent of the administered nitrogen was rapidly lost in the urine, with a consequent large increase in the total urinary loss of nitrogen and a marked and unusually prolonged period of negative nitrogen equilibrium (Wilkinson *et al*, 1950 a)
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the time of their loss, but since the administered potassium also is excreted, this does not result in any gain in the potassium content of the body. The close renal conservation and low urinary output of sodium and chloride have been interpreted as an indication for the provision of supplements. The maintenance of a normal level of intake of sodium and chloride during the first week after

injury leads, however, to the retention of large quantities of both elements. Water also is retained to maintain isotonicity in the body and results in expansion of the volume of extracellular fluid, this may be so large as to cause oedema, and the transfer of sodium into the intracellular fluid may cause disturbance of cellular function

During the anabolic phase the consumption of an abundant and adequate diet is essential for full recovery, this is the period of convalescence when there is a particular need for protein and probably also additional potassium and some vitamins such as ascorbic acid and riboflavin These requirements are supplied by a good mixed diet containing adequate quantities of high quality protein, fresh fruit and vegetables. In severe injuries such as those due to extensive burns, the continued loss of exudate from the extensive raw surfaces results in unusually marked wasting of the body, especially of fat and skeletal muscle, Levenson and Evans (1951) and others believe that much of this wasting can be prevented by the early institution of high food intakes and have recommended that continuous gastric drip-feeding should be started within a few days of injury as soon as it can be tolerated.

There is a limit to the tolerance of the patient to this kind of procedure, and nausea and vomiting may be persistent if too much carbohydrate and protein are forcefully fed by stomach tube. While enthusiasm must be tempered with humanity and realism, there is no doubt that much unnecessary and undesirable starvation is too often permitted to persist long after the patient could reasonably have started to eat ordinary food and drink palatable but concentrated liquid mixtures.

In the absence of abnormal fluid loss, such as that caused by repeated gastric aspiration, the recovery of a patient from a major operation or severe accidental injury is usually uneventful, provided that the consumption of food is resumed as soon as appetite returns, the parenteral administration of fluid, calories or protein is not required. After injury human beings, like other animals are able to tolerate a period of starvation for water and food during which the body lives on and heals from materials derived from its own substance, if excessive bleeding or infection does not cause death, survival depends on the patient having at the time of injury sufficient bodily resources and the hormonic means of using them to live long enough to heal.

CHAPTER VI

SHOCK

THERE has been much criticism of the continued use of the term "shock" to cover the varied circulatory disturbances which may follow injury. The value of the term depends on the use of qualifying phrases indicating the underlying cause of the circulatory disturbance; for example, shock due to loss of plasma or shock due to bleeding. When thus qualified, the term is probably more useful and widely understood than any of the alternatives which have been suggested.

CLASSIFICATION

The most important factor concerned in the production of circulatory disturbances after injury is a reduction in the volume of blood in active circulation in the body. This may be due to bleeding with the loss of whole blood from the vessels (shock due to blood loss) or of plasma from the unusually permeable capillaries in burned or scalded tissues (shock due to plasma loss). The volume of blood in active circulation may also be reduced when blood accumulates in dilated blood vessels in one part of the body as the result of a nervous mechanism (neurogenic shock). Shock was formerly classified according to the time of onset. All shock appearing within two hours of injury was called primary shock and was assumed to be due to an ill-defined nervous mechanism. All shock which appeared more than two hours after injury was called secondary shock and was thought to be due to blood or plasma loss, the action of toxins or the products of tissue breakdown, and other factors. Severe bleeding may cause shock within a few minutes of injury, and pain arising during the examination of dressings or splints may cause neurogenic shock several hours after injury. Shock should therefore be classified according to its main cause rather than to the time of its onset or diagnosis, into two main types:

(1) Neurogenic shock or vasovagal collapse
(2) Shock due to fluid loss, either blood or plasma.

Neurogenic Shock.—This may follow accidental bleeding or the bleeding of transfusion donors, it may be associated with emotion, pain, the manipulation of injuries such as fractures, or with change in posture. The characteristic features are pain a fall of systolic blood pressure to about 60 mm Hg (the diastolic pressure may be too low to be recorded), slowing of the pulse rate to 40 or 50 per minute, coolness and pallor of the skin, especially on the face, hands and feet. There may be yawning nausea, vomiting and fainting This reaction is due to vasodilatation of the arterioles of the skeletal muscles by nervous impulses mediated through autonomic fibres in the mixed peripheral nerves (Barcroft *et al.*, 1944) Amongst blood donors the incidence and severity of the reaction are related to the quantity of blood which is removed, practically all professional donors faint after the removal of 1200 to 1400 ml blood Recognition of this disturbance depends on observation of the very slow pulse rate combined with the low systolic pressure.

Recovery generally follows recumbency, but this may make little difference. The administration of a vasoconstrictor drug such as Methedrine (N methyl amphetamine) usually constricts the dilated vessels in the skeletal muscles and returns the blood from these vessels to active circulation. When this disturbance follows a surgical operation, the blood loss may have been small, but it may accompany severe blood loss and the clinical picture may then be modified by the effects of the bleeding, and diagnosis is made more difficult.

Circulatory disturbances of the vasovagal type are becoming more common immediately after operations in which relaxant drugs have been used, this has not been satisfactorily explained but may be related to the repeated administration of small doses of pethidine It is possible that rapid recovery from a light general anaesthetic, the cessation of assisted respiration and a return to perhaps rather light spontaneous respiration, may combine to increase the severity of the circulatory effects of drugs which diminish vagal tone. In addition, occasionally blood pressure may be maintained during anaesthesia by carbon dioxide retention, caused by inadequate assisted respiration, the subsequent elimination of carbon dioxide being followed by a fall in blood pressure. In these circumstances the administration of a vasoconstrictor drug usually increases the difficulties of judging the state and

progress of the patient, and increases confusion, especially if the blood pressure falls again when the effects of the Methedrine decline.

Shock due to Loss of Blood or Plasma.—Because there is loss of blood or plasma or of both out of the vascular system into the wound or damaged tissue, there is reduction in the volume of blood in active circulation within the vessels. It is now generally agreed that this extravascular loss of blood or plasma is the most important single factor in causing the syndrome of shock, and it follows that rapid and complete replacement of this loss is the chief factor in the successful treatment of shock due to this cause.

In **shock due to bleeding,** the rate of loss and the total volume lost are both important factors. The rapid loss within a few minutes of 2 pints (1·12 litre) of blood may cause severe circulatory disturbance; repeated small losses of blood spread over a longer period of time, especially during anaesthesia, may however be less well tolerated than a single rapid loss of the same total volume. Compensation for acute blood loss by the formation of red cells is slow, and restoration of volume by transfer of interstitial fluid into the vessels is partial and takes 24 hours or more to be effective. Reflex vasoconstriction reduces the capacity of the vessels and redistributes the remaining available blood to maintain an adequate blood supply to those organs and tissues on which survival of the organism primarily depends. This implies intense vasoconstriction in the less essential organs or those which, because of less highly specialised function, can continue to exist at a lower rate of oxygen utilisation. The general vasoconstrictor effect of blood loss may be overcome locally by a strong stimulus like heat, as in the improvement in the rate of venous flow brought about by warming the limb before transfusion or by warming the fluid to be injected.

In assessing the condition of a shocked patient and the rate and direction of change in his condition, some direct index of the circulatory state is needed. The best would probably be a technically easy means of rapid and accurate measurement of total blood volume; at the present time no method exists which is suitable for general use in the ward by persons who have not learned the required special techniques It is still necessary, therefore, to make a clinical judgment based largely [illegible] perience The clinical data required are a history of th[illegible] indication[illegible]

of the amount of blood lost, the nature and extent of the injuries, the systolic and diastolic blood pressure, the pulse rate and the colour and temperature of the skin in various sites, the filling of the superficial veins, and the rate of return of skin colour after digital compression. *By repeated observation of these clinical* features at intervals of half an hour or less during critical periods of rapid change, it is possible to build up a picture of the disturbance in a particular patient. No two shocked patients are ever wholly alike, and such direct observations enable a closer assessment to be made of the reaction of any individual to a particular injury than any system based on a full description of many types of reaction.

The effects of an acute loss of blood vary greatly In a fit young man with an initial blood volume of about 8 pints (4 5 litres) up to a pint of blood may be lost without much change in the colour or temperature of the skin pulse rate or blood pressure.

After 2 pints of blood have been lost, cutaneous vasoconstriction leads to pallor and coldness of the skin, and the pulse rate rises to about 100 per minute, but there may be little change in blood pressure. When the blood loss exceeds 3 pints, the increasing vasoconstriction causes pallor with cyanosis, which affects even the lips the pulse rate usually rises rapidly and the systolic blood pressure falls below 80 mm Hg, the diastolic pressure may be too low to be recorded and later the pulses may become impalpable The patient is often mentally alert, garrulous and perhaps excessively apprehensive. As his general condition deteriorates he may become restless exhibit air hunger and even maniacal excitement. In the terminal stages, after rapid loss of very large quantities of blood, respiration becomes gasping and spasmodic, consciousness may be lost and death may seem to be imminent. Provided that this state is of only short duration, complete recovery may follow rapid replacement of the lost blood by transfusion.

The vasoconstrictor reaction may at times exceed the exact degree of intensity necessary to compensate for the particular fluid loss which has occurred, this causes what is known as the *hypertensive response or reaction.* This is more common in young subjects, especially children, pallor is usually marked, the extremities are cold, the pulse rate is increased, and the blood pressure is raised above normal, sometimes as high as 170 to

180 mm. Hg systolic and 100 mm. Hg or more diastolic. Th hypertension may be suddenly succeeded by a profound fall blood pressure, especially if the patient is warmed. A hypertensi reaction should therefore always be an indication for caution an careful observation. Patients who have been excessively chille are in general more difficult to resuscitate; it is often hard predict how they will respond.

The commonest type of accidental injury giving rise to shock a wound of the limbs, especially in association with a compoun fracture. The severity of the shock is related directly to th volume of blood which is lost from the circulation, which in tur is usually related to the mass of muscle involved. Shock therefore most severe in association with large lacerated wounc of the upper thigh and buttocks, and in compound fractures of th shaft of the femur. Grant and Reeve (1941) suggested that quantitative estimate of the tissue damage, and so indirectly of th blood loss, might be obtained by estimating wound size in unit of the size of the open hand or closed fist, which is about equal t 500 ml. In closed fractures, blood loss may also be calculate from measurements of change in the length and girth of the lim compared with those of the uninjured side. Bleeding is du chiefly to laceration of the surrounding muscle bellies by the sharp and jagged ends of the broken bone. Fractures of the femoral shaft associated with severe violence may be followed by the loss of up to 5 pints of blood, bleeding is increased by movement of the fractured bone or the affected limb and is minimised by early immobilisation with some traction in a suitable splint. Clarke *et al.* (1955) have confirmed this well-known quantitative relationship between swelling of an injured limb and blood loss into it by measurements of limb volume and total circulating blood volume. In wounds of the limbs, division of main vessels is comparatively uncommon in peacetime, but extensive venous bleeding may follow superficial lacerations of the arms caused by pushing hands through windows

Abdominal wounds are a common cause of severe blood loss during warfare, but in civilian practice their incidence varies widely in different countries and even districts. Bullets and other missiles with a high initial velocity may injure any abdominal organ and often pursue unexpected courses after penetrating the abdominal wall. Because of the frequency with which

mesenteric vessels are divided, severe blood loss is common, but injuries of the great vessels within the abdomen are comparatively rare. Before laparotomy, therefore, a hopeful attitude should be maintained towards all cases of intra abdominal bleeding Direct blunt injury to the abdominal wall and lower chest wall may cause severe laceration or rupture of the liver kidney or spleen, with subsequent immediate rapid and extensive bleeding, or concealed or delayed bleeding In all these injuries the cause of shock is predominantly loss of blood, and recovery should follow timely arrest of the haemorrhage, combined with adequate replacement of the lost blood.

Shock due to plasma loss follows injury by burning or scalding In the injured area the capillaries become unusually permeable and plasma leaves the vessels and accumulates in the interstices of the tissues, there is also a large increase in lymph flow out of the injured tissues. Evidence of plasma loss can be seen in superficial blisters and in the exudation of plasma on the raw surface when blisters have been broken, there is also a larger loss into all the damaged tissues causing an inflammatory oedema, which is conspicuous in the face and on the back of the hands. The net result, a local increase in interstitial fluid, is due to fluid leaving the vessels more rapidly than it can return, either by re-entering capillaries directly or by returning through the lymphatic vessels. The local swelling which results is limited by rising tissue tension as well as by the limited duration of the altered permeability of the capillaries. This inflammatory swelling is a dynamic exudate in which there is continuous exchange of the constituents between the exudate and the intravascular fluid and at least temporarily it is the potential destination of much of any fluid which may be injected into the body The formation of this exudate diverts from the remainder of the body a part of the extracellular fluid and some of the plasma protein and thus, by increasing the volume of distribution of the plasma in the body, decreases the proportion of the total plasma volume which at any moment will be found within the blood vessels If this plasma loss is replaced by the transfusion of plasma, a proportion of the small plasma proteins, albumin and possibly also α and β globulins, which are thus added are liable to be lost into the exudate. The effect of plasma on the shock state is therefore not directly proportional to the volume administered. Gum saline and dextran

nervous stimulation. The shocked patient is peculiarly sensitive to changes in posture and position and tolerates badly sudden shifts or rolling, rapid levelling of the table at the end of even a short operation may cause marked deterioration in the condition of a shocked person. Gentleness and the elimination of unnecessary manœuvres are essential during operation on severely injured patients The shorter the duration of the operation consistent with thoroughness and gentleness the better, but speed alone is not enough, traction on mesenteries and interference with the upper abdominal organs cause depression of blood pressure, presumably by autonomic reflexes.

Toxic and Infective Factors.—The cause remains unknown of the severe circulatory depression which is such a common feature of advanced bacterial or biliary peritonitis, pancreatitis or septicaemia In severe peritonitis the circulatory disturbance develops gradually, the skin of the extremities becoming cold and reddish purple in colour, with little change and a very slow return of colour on compression, the systolic blood pressure may fall below 60 mm. Hg, the diastolic pressure can seldom be measured and the pulse may be so fast as to be uncountable. In between periods of restless drowsiness or coma the patient may be acutely alert and often appears to understand how serious his condition has become. As Theron and Wilson (1949) pointed out, the alterations in the red cell and plasma volumes of such patients are not at all closely related to their clinical condition, nor does the transfusion of blood, plasma or dextran, or the intravenous administration of saline, produce a lasting or even a predictable improvement in blood volume and the circulatory state In spite of a very large amount of experimental investigation there is still no certainty regarding the identity and mode of action of such toxic factors as have been shown to be capable of inducing circulatory failure resembling that seen in patients with various kinds of peritonitis.

The livid cold skin suggests that the capillaries are fully dilated and filled with stagnant red cells; the use of noradrenaline and other vasoconstrictor agents, even when combined with the transfusion of blood or dextran, seldom produces any lasting circulatory improvement. Fine (1954) on the basis of a long series of animal experiments put forward the view that the fundamental disturbance is due to the blockade of the reticulo-endothelial system by the toxins of *E. coli* and *Cl welchii.* In animals suffering initially

from haemorrhagic shock he and his colleagues were able to prevent the toxaemic phase by the preliminary elimination of the organisms from the intestinal flora, by treatment with a broad spectrum antibiotic. Although the features of the anatomical changes in the alimentary tract found by Fine and his colleagues do not commonly occur in patients with peritonitis, the systemic disturbance is similar The remarkable clinical improvement which follows the very early use of transfusion in patients with extensive peritonitis associated with vascular hypotension also resembles the response which Fine has been able to demonstrate in toxaemic shock in the experimental animal.

Adreno-cortical Factors—Occasionally after injury or operation, or during severe infections circulatory failure is associated with extensive bleeding into both suprarenal glands. Sudden acute circulatory failure may also occur during and several days after operation on patients who have for long periods been treated with cortisone or similar adrenal hormones, or when, after bilateral adrenalectomy, the maintenance dose of cortisone is inadequate. The normal outputs of ACTH and of cortical hormones by the adrenals, are believed to be determined by chemoreceptors in the hypothalamus which are sensitive to the concentration of cortical hormones circulating in the extracellular fluid. The weight of the adrenal glands, and their sensitivity to injected ACTH, are both reduced by the prolonged administration of adrenal cortical hormones, which reduces the need for production of hormones by the adrenal glands According to Christy *et al* (1956), the degree of adrenal suppression is more closely related to the duration of treatment than to the dosage, but there is wide variation between individual patients and in the duration of the refractory period which follows stoppage of the hormone treatment.

In patients with Addison's disease, or those whose maintenance dose of cortisone is inadequate, circulatory collapse is usually preceded by an insidious deterioration in appearance and condition, accompanied by bad temper and irritability, poor appetite and nausea or vomiting Although these changes are noticed, the subsequent sudden failure of the circulation, with a sharp fall in blood pressure, poorly filled veins and rising pulse rate often comes as a surprise. By withholding the maintenance dose of cortisone from adrenalectomised patients Hills *et al.* (1953)

showed that this type of circulatory collapse is associated with a loss of sodium from the extracellular fluid and reduction of the volumes of intracellular fluid and plasma They thought that sodium and its accompanying water were lost into the cells or the connective tissue gel. This type of circulatory disturbance responds rapidly to the administration of cortisone or hydrocortisone, without the administration of sodium chloride or water, and thus is probably due to an alteration in the distribution of sodium and water between the cells and their environment. A similar type of circulatory disturbance may occur during, or several days after, operations on patients to whom adrenal cortical hormones have been administered for a long time. In such patients a choice must be made between the prophylactic use of corticoids before and after operation in all cases, or of waiting for the occurrence of a circulatory disturbance, which is then treated by the injection of cortisone or hydrocortisone. The latter combined with careful observation is probably the more desirable course to adopt.

DIAGNOSIS

In accidental injuries it is important to make a complete examination of the whole body as soon as possible Clothing should be cut off, note being made of the quantity of blood on the garments, dressings and stretcher; when the injuries are very extensive and shock is very severe, it is usually wise to leave the patient undisturbed until blood volume has been increased by rapid transfusion. Fractures should be splinted and bleeding controlled by pressure with pads The most important indication of the amount of blood lost is the size of the wound, for it is seldom that blood soaking of clothes or dressings indicates accurately the whole volume which has been lost A large wound is usually a good indication for starting a transfusion as a precaution (Table XVIII). It should be remembered that changes in blood pressure and in the cutaneous circulation lag behind changes in blood volume and are late indications of deterioration Nevertheless, when combined with evidence of vasoconstriction such as pallor and coldness of the skin, and an increased pulse rate, a systolic blood pressure of 100 mm. Hg is an indication of moderate shock; of 80 to 100 mm. Hg of severe shock and of below 80 mm Hg of

very severe shock. Progressive decline of the blood pressure w accompanied by evidence of vasoconstriction indicates contin bleeding or plasma loss, such deterioration can usually be arre only by rapid transfusion and suitable surgical treatment. R lessness, if not caused by pain, is usually a sign of progres reduction in blood volume and should be treated by immed transfusion. In general, it is wise to transfuse all patients wh

TABLE XVIII

Diagnosis of Shock

Type	*Volume of loss*	*Skin*	*Blood Pressure*	*Pulse Rate*
Neurogenic	Varies	Warm, pale	<60/?	<80
Blood or plasma loss	<2 pints	Unchanged	>100/60	80-10
	2 3 pints	Cool, pale	100-80/60	100-12
	3 5 pints	Cold pale (cyanosed)	<80/?	>12
	>5 pints	Cold, pale (cyanosed)	<60/?	>12
Hypertensive response	Varies	Cold, pale	>140/100	>10

systolic pressure falls below 80 mm. Hg because of bloo plasma loss.

The chief exception to these recommendations is in the ca vasovagal or neurogenic shock. The distinction between v vagal shock and that due to blood or plasma loss can usuall made on the blood pressure level, pulse rate and the state of skin. In vasovagal shock the systolic blood pressure ma 60 mm. Hg and the diastolic pressure too low to be recor these changes are associated with a slow pulse rate in the regi 40 or 50 beats per minute and pale but warm skin. In shock to loss of blood or plasma the systolic blood pressure is not c as low as 60 mm. Hg the pulse rate is fast, 100 to 120 and r even 140 beats per minute, the skin is pale and cool or cold. vasovagal reaction may develop during or soon after sur operations and general anaesthesia, because of blood loss, a m

picture is produced, the blood pressure being unexpectedly low for the observed blood loss and the pulse rate faster (60 to 80 per minute) than would be expected for a pure vasovagal reaction; the administration of a large dose of atropine may also partially prevent the usual bradycardia.

The unusual combination of a normal blood pressure with severe injuries is usually an indication of a hypertensive response, and special caution is required; the pulse rate is usually raised and the skin is pale and cold When a small wound is associated with an unexpectedly low blood pressure, the pulse rate often provides the clue to a correct diagnosis. If the pulse is very slow, a vasovagal reaction is indicated and external blood loss has probably been very small. *If the pulse rate is fast, it suggests either a poor* vasoconstrictive response or the impairment of this by heating. Another possiblity is that severe blood loss has occurred and may have been due to injury to a large artery or vein.

TREATMENT

General Principles.—Except to a very limited degree in the first two or three hours after injury, delay is not of value in the treatment of shock. When patients reach hospital very soon after injury it is usually wise to allow them a short period for stabilisation before surgical treatment of the injuries is undertaken. Apart from this reservation, the sooner the lost blood is replaced and the injuries are treated, the better is the prognosis.

The ratio between surface area and weight is high in babies and diminishes as body weight increases. The cutaneous circulation is thus more important in children than in adults; superficial injuries such as burns have a more serious effect in children than in adults and interference with compensatory vasoconstriction by excessive warming is more harmful. On the other hand, children and young adults respond more readily and completely to thorough treatment of severe shock and extensive injuries than do older patients.

Wounds in certain situations are associated with a bad prognosis because of the associated large blood loss and the difficulty involved in adequate haemostasis and treatment of the wounds. Such wounds are those of the buttock and upper thigh and the internal lacerations associated with severe and bilateral fractures

of the pelvis. Injuries resulting in the pulping of large masses of muscle lower in the thigh or in the calf are associated with severe shock, which may be resistant to transfusion until the pulped muscle has been excised Multiple limb injuries, such as compound fractures, are sometimes best treated in stages, for the additional blood loss associated with excision and suture of the wounds may render immediate manipulative reduction of the fractures unduly dangerous, it may sometimes be wiser merely to immobilise the limbs after wound treatment and to delay accurate reduction of the fractures for one or two days Intra-abdominal injuries always carry a serious prognosis because of the risk of secondary complications such as peritonitis and ileus Chest injuries alone usually do well and shock is not severe, but when combined with abdominal or limb injuries they impose some limitation on the freedom with which blood and other fluids may be transfused.

It seems hardly necessary to emphasise that the treatment of patients shocked by blood loss from severe or extensive injuries comprises more than just the replacement of the lost blood. It is essential to visualise at the outset the whole process which may be involved in the treatment of a particular patient. An attempt must be made to predict how much blood will probably be necessary, how long resuscitation may take, and the amount of further bleeding and injury which may be inflicted by operation Once having made such an assessment as treatment progresses the surgeon must be prepared to modify the original estimates and decisions according to the response of the patient, for the shocked patient is liable to rapid deterioration or improvement. The management of the severely wounded patient demands continuous close attention, repeated measurement of pulse rate and blood pressure, and observations of the cutaneous circulation and general state. The sooner operative treatment can be carried out the better, and damaged tissue should be removed as soon as possible. When a number of shocked patients are admitted at the same time, decision as to priority depends to some extent on the nature of their injuries, but the rate at which they can be resuscitated may vary and may prove the more important factor

In ideal circumstances the surgeon should conduct the resuscitation of the patient as well as the operative and post operative treatment. Close co-operation between surgeon and

anaesthetist is essential, and if the surgeon is unable personally to supervise resuscitation, the anaesthetist is the best alternative person to do so. It is usually easy to recognise when the condition of a patient has been restored to normal by measuring pulse rate and blood pressure and by observing the other signs of circulatory improvement, and with reasonable precautions the subsequent management of such patients does not give rise to difficulty.

Unfortunately, many patients with severe injuries do not respond so completely or in a consistent fashion to transfusion, and in these circumstances difficult decisions must be made. For example, a patient with a gunshot wound of the abdomen may respond well to the rapid transfusion of three pints of blood during a period of 45 minutes, then blood begins to flow from the small wound of entry, and blood pressure, which had risen from an unrecordable level to 100/50 mm. Hg, once more falls. This deterioration continues in spite of an increase in the rate of transfusion. It is obvious that intra-abdominal bleeding has restarted, or has increased in rate and equals or exceeds the rate of replacement by transfusion The only worthwhile course is to proceed at once with laparotomy in the hope of being able to control the bleeding vessels and then by rapid replacement of the lost blood by transfusion to make the remainder of the operation feasible and safe. An equally urgent decision may be required after rupture of the spleen or kidney, laceration of the liver or in severe limb injuries where there is a large quantity of mangled muscle. In the course of resuscitation of such patients a peak of condition is reached which is soon followed by deterioration; although later by increasing the rate of transfusion a further period of improvement may be achieved, the first peak of improvement is invariably the highest. The optimum time for operation is just before this peak is reached; its recognition demands calm assessment, firm decision and a willingness on the part of both surgeon and anaesthetist to accept the unusual risk.

General Measures.—After arrival at hospital, a short period of rest for the patient is often followed by a marked improvement in general condition. It is important that he should be made as comfortable as possible. Splints and dressings may require adjustment and the foot of the bed should be raised on 10-inch blocks. Reassurance is of the greatest importance to the patient, and he should be told something of the nature of his injuries.

Morphine should be administered only for the relief of pain, and should always be given in moderate doses (not more than ¼ gram) by deep intramuscular injection. Absorption from the subcutaneous tissues is delayed in severe shock and the simultaneous absorption of repeated doses when blood flow is improved by transfusion may cause morphine poisoning. The slow intravenous injection of morphine is permissible, but is dangerous in severely shocked patients because, on account of redistribution of the circulating blood by vasoconstriction, an unusually large proportion of the dose may reach the central nervous system.

If possible, any wet clothing should be removed and the patient should be placed in a warmed bed or in blankets. The best way to restore the peripheral circulation in a shocked patient and to make the skin warm is to replace the lost blood or plasma by transfusion. To heat such a patient with hot water bottles, electric blankets or "shock cradles" causes vasodilatation and is harmful, since it impairs the vasoconstrictive redistribution of the diminished blood volume on which survival may depend. Provided the patient is covered with enough blankets to retain body heat, he will become warmer as he is resuscitated by transfusion.

Thirst is best alleviated by sucking gauze moistened with cold water. Large drinks of water or tea will be greedily consumed by the severely shocked patient, but usually result in vomiting, which is particularly dangerous during the induction of anaesthesia. To avoid this danger, patients who have been allowed to drink should have their stomachs aspirated before anaesthesia is induced. Unless there has been a long delay between injury and arrival at hospital, few civilian patients in temperate climates suffer from such severe deficiency of body water, apart from that due to bleeding or plasma loss, that intravenous infusion of glucose solution or saline is required before operation. When there has been delay, the best pre-operative treatment is still probably adequate blood transfusion.

In hot climates and especially in the tropics, water loss by sweating may require replacement even before operation, but it is also important to reduce water loss as much as possible by shading the patient from the sun and by cooling him with fans. Intravenous infusions of glucose may be necessary if there is vomiting or if the nature of the wounds prevents drinking. Saline should be used with caution because of the retention of sodium and

associated water by the injured subject. Sweating during operation should be minimised by cooling the theatre, by dispensing with rubber sheeting and by reducing towel draping as far as possible.

Vasovagal Syndrome.—The significance of this disturbance is often difficult to determine, especially when it occurs in association with severe injury or blood loss. Some improvement usually, and complete recovery occasionally, follows elevation of the foot of the bed. When a vasovagal disturbance is combined with severe blood loss, for example just after a major abdominal operation, it is unwise to use vasoconstrictor drugs to combat the vasovagal element in the combined disturbance. Close observation combined with adequate replacement of any accompanying blood or plasma loss is probably the wisest course to adopt. These drugs cause a temporary elevation of blood pressure and of heart rate lasting 2 or 3 hours, but if when these effects pass off the vasovagal disturbance continues, the resulting secondary fall in blood pressure may be difficult to interpret. Instead of employing a vasoconstrictor agent, the foot of the bed should be raised on blocks and a close watch kept for change in the general condition; deterioration caused by continued bleeding can usually be readily recognised The persistence of a low blood pressure for several hours after operation does not appear to do any harm and may reduce post-operative bleeding.

Restoration of Blood Volume.—Transfusion is indicated (1) in all patients with a pulse rate above 100 per minute and a systolic blood pressure below 80 mm. Hg, and in other patients when there is any doubt, or if spontaneous improvement does not result from simple general measures; and (2) in the presence of severe injuries with tissue damage exceeding the size of two fists in volume, even when blood pressure is within normal limits and the pulse rate is not raised.

The lost fluid should be replaced as completely and as rapidly as possible, blood with blood, and plasma with dextran. Complete replacement is usually indicated by the restoration to normal of colour and temperature of the skin, peripheral blood pressure and venous filling, and by the reappearance of bleeding in the wounds. The two factors, rate and volume, are to some extent interdependent. The slow transfusion of a very large volume of blood may be ineffective when the rapid injection of a

small volume would have produced marked improvement The sooner transfusion is begun, the more likely is the rapid administration of a small volume of fluid to be effective. Delay can be avoided by starting replacement with dextran while blood is being cross-matched, dextran may also be used instead of blood when only limited quantities of blood are available, or when only small volumes of replacement fluid are required (up to 1 litre or 2 pints) As the result of experience in Korea, Prentice *et al* (1954) advocated the frequent use of very large transfusions of blood in severely injured patients. However, in spite of using up to 30 pints of blood within 24 hours of injury, they were unable to overcome the deficit in blood volume after transfusion and operation in their patients on the contrary, although the clinical features of shock were seldom seen, the blood volume deficit after transfusion became larger as the volume of blood transfused was increased. This disparity has not been explained and at present it does not seem as if their advice should be generally adopted.

In severe shock the fluid should be injected as fast as it can be made to run through the size of needle employed. It is essential to use the largest needle, cannula or polyethylene catheter that can be inserted into a vein. When veins are in such a tightly constricted state that they cannot be punctured readily with a large needle, to avoid delay a vein should be exposed under local anaesthesia and a metal cannula or polyethylene tube inserted, even in very young children, Size 2 polyethylene tubing is the finest calibre which should be employed and not less than Size 3 should be used in older patients. It is important to reduce resistance to flow to a minimum by making the segments of narrow calibre, such as cannulas and needles, as short as possible. In addition, turbulence in the liquid should be reduced by tapering the junctions where the calibre of the tube changes Disposable sets of delivery tubing and containers have been designed incorporating these improvements Pressure may be applied to the air inlet of the standard transfusion bottle at the risk of an air embolism, whereas with a plastic container pressure can be applied externally with complete safety by wrapping the plastic container in a sphygmomanometer cuff which is then inflated. Venous spasm can be reduced by warming the limb and the blood or other fluid before administration. Especially in abdominal injuries,

veins in the arms should be used in preference to those in the legs. By these means a pint of blood may be injected in five minutes, but such rapid replacement should not be continued after the systolic blood pressure has been raised to 100 mm Hg. The total volume to be given to a particular patient depends on the quantity which has already been lost, on whether blood loss is continuing and on the response to treatment.

Recently, however, it has been recognised that the treatment of severe blood loss by rapid transfusion is not invariably successful. Firt and Hejhal (1957) have described three types of failure of response to such treatment. The largest number of failures are due to giving too little blood too slowly or too late, a combination which is rarely unavoidable In some patients cardiac failure may appear during transfusion, while in others a deterioration in general condition is accompanied by a rising venous pressure. They have produced experimental evidence that both these types of disturbance may be due to citrate intoxication, rather than to the rapid rate of transfusion Disturbances in the electrocardiographic tracing during the transfusion of citrated blood were reported by Furman *et al.* (1951), who observed a progressive increase in the QT interval, an increased ST segment and a reduced amplitude of the T wave, which were abolished by the injection of calcium gluconate The onset of citrate intoxication seems to be related to the rate of transfusion, but because citrate is excreted in the urine, or metabolised in the liver and muscles, is also more likely when there is severe disturbance of hepatic or renal function. The possibility of citrate intoxication should be considered when the response to the rapid transfusion of a large volume of blood is unexpectedly disappointing, especially in patients with poor liver function or during whole body cooling, and during exchange transfusions in erythroblastic infants

Both in animals and in the human subject of all ages citrate intoxication has usually been associated with a very fast rate of transfusion Nonetheless, at least in the early stages of replacement of a large loss of blood, rapid transfusion is an important factor in survival. Gurd and Gardner (1955) found that up to 75 per cent. of the lost blood should be replaced very rapidly but the remainder should be given more slowly if cardiac failure associated with a rising venous pressure was to be avoided. Adams *et al* (1944) expressed the opinion that in adults transfusion at the

rate of 1 litre an hour was usually safe, and this has been confirmed by Bunker *et al* (1955)

Even when blood volume has been fully restored before the operation is begun the intravenous infusion should be continued slowly during and for a time after operation to enable the rapid replacement of any further blood loss to be made without delay During the operation, the general progress of the patient is best judged by repeated measurement of blood pressure, pulse and respiration rates and by observation of the state of the peripheral skin circulation The colour of the blood and the rate of bleeding in the operation wound may provide some additional information. Most of this must necessarily be done by the anaesthetist, who is also in the best position to assess the effects of the anaesthetic agents on the circulatory and general state of the patient. It may be necessary at times to stop manipulation in the upper abdomen or of a fractured limb because of the neurogenic hypotension which this may cause. Whatever may be their value in deliberate surgery, anaesthetic techniques and drugs such as spinal analgesia and the methonium compounds, which cause marked hypotension, are dangerous and should not be used in severely injured patients. They are dangerous because replacement of lost blood may have been inadequate and the residual vasoconstriction on which circulatory efficiency depends may be abolished by these hypotensive agents This risk is not outweighed by the possible reduction of operation blood loss at a lower blood pressure.

After operation, a slow intravenous infusion of glucose solution is usually continued for 12 to 24 hours so that any further blood loss may be replaced without delay In chest injuries, only the minimal quantity of blood should be employed and the infusion should be stopped as soon as blood loss has been replaced. In abdominal injuries involving the alimentary tract, the oral intake of fluid is usually restricted or stopped for 24 hours or more and gastric aspiration is instituted, fluid intake is generally maintained by intravenous infusion until the oral intake of fluid can be resumed

In burns, the blood pressure should be restored by the rapid intravenous injection of dextran and thereafter the vein kept open by a very slow infusion of glucose solution, further dextran may then be administered immediately it is needed and the basal requirements of water can be satisfied by the glucose infusion.

In deep burns there may be sufficient destruction of red blood corpuscles by coagulation in the burned tissues to warrant replacement by whole-blood transfusion The former reluctance to use whole blood under any circumstances in the treatment of shock due to superficial burns has been shown to be unfounded. For the oligaemia associated with peritonitis, ileus and strangulation of intestine, blood should be used.

INTRA-ARTERIAL TRANSFUSION.—It was claimed by Kohlstaedt and Page (1943) that after severe haemorrhage the intra-arterial injection of blood would raise the blood pressure more rapidly, and with smaller volumes of blood, than was the case with intravenous transfusion. They and others have suggested that the circulation in the coronary and cerebral arteries is more readily maintained and that the whole arterial tree is more easily filled when lost blood is replaced by intra-arterial transfusion, but the evidence for this is not entirely satisfactory. There is no evidence that myocardial failure due to an inadequate coronary blood flow plays more than a terminal part in death from bleeding. Indeed the continuing vigorous pulsation of the exposed heart whose chambers have been emptied by bleeding from a large peripheral artery must be one of the most impressive physiological demonstrations. An experimental comparison of the effects of intravenous and intra-arterial transfusion was made by Case *et al.* (1953) in the dog. They found that, after bleeding, transfusion into the femoral artery did not increase the coronary arterial circulation rate and was not more effective in restoring femoral arterial blood pressure to normal than was intravenous transfusion of a similar volume of blood at the same rate, and others have independently reached the same conclusion.

The radial or dorsalis pedis artery has been most often employed for the injection, but the aorta has also been used when severe bleeding has occurred during abdominal operations. When a peripheral artery is used, a cannula is inserted towards the heart and is connected to a delivery set w[illegible] [illegible]ludes a mercury
manometer and a pressure pump. [illegible] at
a pressure of at least 120 mm. Hg. [illegible]
prevent the injection of clots and to [illegible]
than two-thirds of the contents c[illegible]
injected under pressure. Gangrene [illegible]
the point of injection has [illegible]

There is no evidence that this method with its cumbers apparatus and greater potential risk is of more use than the and determined treatment of shock by intravenous transfu especially when two veins are simultaneously used. The s of peripheral intra arterial transfusion is limited, its valu doubtful and it cannot be recommended

INTRA-AORTIC TRANSFUSION may have a limited use in peculiar circumstances of operations on the great vessels, espec the aorta, when the readiness of access permits the imme injection of a large volume of blood into the aorta under d vision

PREVENTION OF SHOCK IN DELIBERATE SURGE

General Measures.—The patient should be brought to op tion in the best possible condition and all unusual and vi methods of preparation such as repeated drastic purgation w might disturb his fluid equilibrium should be avoided. Res tion of food and fluid intake should be reasonable and mol maintained as long as possible. Taylor *et al.* (1945) showed when healthy young subjects are confined to bed and kept at for two weeks blood volume falls by 10 per cent. The import of mobilising patients who have been bed fast for several w before submitting them to surgical operation is well recogni a delay of 10 days or so for physical rehabilitation is well re by the improvement in morale as well as in circulating b volume and pulmonary function. Blood volume should be stored and anaemia corrected by transfusion. In wasted sub it is probably better to use packed cells than whole blood whichever is chosen an interval of at least three days shoul allowed between the last transfusion and operation. Disturba of water sodium, potassium, chloride or bicarbonate equilibi should have been corrected and an interval allowed for stabi tion before the day of operation.

Hypotensive procedures designed to limit blood loss have l used for many years. Spinal analgesia produces arterial hy tension by vasodilatation in the distribution of the spinal segm affected by the drug The resulting diminution in bleeding in operation wound has been of value in many operations, and extension of this method to very high (T2) spinal block has

specific gravity of the urine fall and acid haematin is found in the dark deposit. After a day or two pigment excretion ceases and casts become more numerous. Urinary output may be low only for 24 to 48 hours and then increase, and the blood urea concentration may be raised only for a short time. With more severe renal damage, urinary output is reduced for up to a week before a diuresis occurs and the blood urea may rise to a very high level. Renal function recovers slowly, and clearance may not return to normal limits for several months. About the end of the first week after injury more than half the patients die of cardiac arrest due to the high extracellular potassium concentration. At autopsy, the cortex of the kidneys is pale and swollen, but the medulla is dark, and on histological examination debris and pigment are seen in the renal tubules

This syndrome consists of two components: first, the loss of plasma into the crushed tissue after release of compression with the subsequent development of a form of shock due to plasma loss; and secondly, the excretion of oxymyohaemoglobin or metamyohaemoglobin in an acid urine. It appears that the combination of reduced renal blood flow, acidosis and pigment excretion is necessary for the production of the fully developed state.

Treatment is primarily prophylactic If possible before release the victim should be given tea to drink, and alkali as sodium bicarbonate may be given dissolved in water (a dessertspoonful to the pint). After release, the administration of water and alkali should be carefully controlled and restricted if a diuresis does not occur within an hour or two. Patients with severe crush injuries should receive dextran prophylactically before the blood pressure falls. The injured limb should be kept cool by being exposed without coverings. Established oliguria or renal failure should be treated as indicated in the section on anuria (p. 175).

CHAPTER VII

DISTURBANCES DUE TO LOSS OF GASTRO-INTESTINAL SECRETIONS

THE effects of the loss of fluid from the alimentary tract depend chiefly on the rate and total volume of fluid lost. These secretions are derived in the first place from the plasma and so from extra-cellular fluid and large depletions of the extracellular fluid may result from copious vomiting, repeated diarrhoea or fluid loss from an intestinal fistula. To a limited extent such losses can be compensated by the transfer of fluid from the cells to the extra cellular fluid, but this process takes time. When the loss of secretion is large or continuous, the transference of cell fluid makes little impression on the rapid depletion of extracellular fluid volume and does not prevent the onset of oligaemic circulatory failure due to the reduction in volume of plasma and extracellular fluid. When the loss of secretion is less rapid but more prolonged, the effects of the primary loss of secretion combined with the compensatory changes in intracellular fluid and the administration of solutions of various kinds may result in marked distortion of the composition of the body fluids.

The fluid lost seldom consists solely of one type of secretion, but is usually a mixture of secretions from more than one region of the alimentary tract. In addition, the composition of the intestinal secretions varies widely from one individual to another and from time to time in the same person In general it can be said that repeated vomiting leads particularly to the loss of hydrogen ion as hydrochloric acid and so to a metabolic alkalosis but the associated loss of sodium and water also causes reduction in extracellular fluid volume, whereas the loss of secretion from the small and large intestines by diarrhoea or discharge from a fistula leads to loss of bicarbonate as well as of sodium and water, and so to a metabolic acidosis The sodium content of the bile, pancreatic juice and small intestinal secretions is usually high. The concentration of potassium in all alimentary fluids is normally as high or higher than it is in the plasma. Chloride is usually present in high concentration in gastric juice and in low concentration in pancreatic juice. Rapid losses of large quantities of fluid from any level in the alimentary tract lead

to depletion of sodium and water. Repeated losses over a long period, especially if replaced by infusions of saline, glucose solution or other fluids containing little or no potassium, lead ultimately to depletion of potassium as well as of sodium and water.

OESOPHAGEAL OBSTRUCTION

In both benign and malignant disease of the oesophagus progressive obstruction leads to increasing difficulty in swallowing food and fluids. This undernutrition causes a reduction in lean tissue mass and fat (McMurrey *et al* (1955)). These undernourished patients have a poor tolerance for intravenous infusions and for rapid and repeated transfusions of blood or plasma; cardiac irregularity or failure due to overloading is readily produced by even small volumes of fluid.

In complete obstruction of the oesophagus, in addition to starvation for food and water, the patient has to expectorate up to 1500 ml. of saliva per day. Because of their poor tolerance to intravenous infusions, the general state of these patients can best be improved before operation by feeding them through a jejunostomy (see p. 220). Because the intestines are empty and contracted, for the first two or three days only small feeds of 60 ml. should be given every hour. In partial obstruction of the oesophagus it is now a common practice to dilate the stricture, perhaps followed by the insertion of a Souttar tube; the patient is then fed orally with a concentrated liquid diet, usually some form of milk mixture.

Patients with oesophageal obstruction suffer primarily from starvation and so lose potassium proportionately with nitrogen, as the result of the catabolism of tissue protein. There is thus no particular need to replace potassium in excess of protein. Marked improvement in the general state of the patient often follows when a delay of 2 or 3 weeks before operation is employed in feeding a high calorie, high protein mixture with supplements of vitamins. The repeated slow transfusion of 500 ml. of fresh whole blood is another valuable adjunct in the preparation of these wasted people for operative treatment.

Ileus is common after resection of the oesophagus and is generally attributed to reduced intestinal mobility following division of the vagal nerves. When the stomach is drawn up into

the chest and anastomosed to the stump of the oesophagus, delayed gastric emptying is common and the accumulated secretions in the stomach must be aspirated through an indwelling tube passed across the anastomosis Rarely, aspiration of the stomach must be continued for more than a week, there is then additional delay in starting to eat, continued loss of body fluids and prolonged dependence on intravenous infusions for the supply of water and calories. The institution of a jejunostomy, before or at the end of the operation on the oesophagus, permits feeding with a milk mixture to be started immediately after operation, and has the additional advantage that fluid aspirated from the stomach can be filtered and run into the jejunostomy In addition, when disruption of the anastomotic suture line leads to leakage of gastric and intestinal fluids into the drained pleural cavity, the collected drainage fluid can be run into the jejunostomy By thus replacing with little delay the actual fluid which has been lost the development of extracellular fluid depletion complicated by the secondary distortion of the composition of the body fluids due to intravenous therapy can be almost entirely prevented. The use of a jejunostomy before operation on the oesophagus has been opposed on the grounds that it interferes with the choice of a loop of jejunum for anastomosis with the oesophagus, but this can be avoided by making the jejunostomy a few feet lower in the intestine than is usual.

LOSS OF GASTRIC SECRETION

Gastric juice as aspirated from the stomach is a mixture of the highly acid secretion of the oxyntic cells and the more alkaline secretions of the other cells of the gastric mucosa. The proportions of these constituents are very variable, and in particular cases it is undoubtedly wiser to measure the volume of the vomitus or aspirated fluid and the content of potassium sodium and chloride before judging the quantities of fluid and electrolyte which should be administered. Vomiting in pyloric stenosis results in the loss of large quantities of gastric juice containing varying proportions of hydrochloric acid and sodium and potassium chlorides The loss of sodium and potassium leads to a reduction in total body water and extracellular fluid volume, and the loss of hydrochloric acid is followed by a compensatory rise in bicarbonate concentration in the extracellular fluid. If this were all that happens to

these patients it would be easy to understand the cause of their physical disturbance, to measure approximately their depletions and to provide fairly specific treatment with a reasonable expectation of success in most cases.

But the loss of sodium in the gastric juice is soon followed by conservation of sodium by the kidneys with the almost complete disappearance of sodium from the urine of many patients, especially if vomiting continues The urine becomes and remains acid so long as sodium conservation continues. This persistence of an acid urine in association with a low concentration of chloride and a high concentration of bicarbonate in the plasma, or "alkalosis", has been recognised for 30 years. It was produced experimentally in dogs by Gamble and Ross in 1925, and Hartmann and Smyth (1926) studied it in patients. Even earlier, however, in 1923, Haden and Orr had shown that this acidity of the urine could not be satisfactorily treated by the administration of sodium bicarbonate, because of the increased severity of the alkalosis which followed such therapy. It was originally thought that the acidity of the urine was simply an expression of the need to retain bicarbonate to compensate for the loss of chloride by vomiting. Both Gamble and Ross, and Hartmann and Smyth showed that in spite of the acid urine the alkalosis could be successfully treated by the intravenous administration of isotonic saline, and at the same time the *p*H of the urine tended to rise. The urine always contains free carbonic acid in a concentration almost the same as that in the plasma, and when the sodium is being completely conserved there is a tendency for urinary *p*H to fall. Only when sodium again appears in the urine does urinary *p*H rise.

It is unusual for a patient with pyloric stenosis to be able to maintain a normal water content during bouts of vomiting. Extracellular fluid volume is depleted by the loss of gastric juice and can be restored only to a very limited extent, and at the cost of a fall in sodium concentration, by the transfer of water out of cells. The best that can be achieved by this transfer is usually only the maintenance of the depleted extracellular fluid volume until it is further reduced by the next vomit. Since the water requirements of patients who vomit repeatedly cannot be adequately satisfied by drinking, water is lost from the intracellular fluid. This intracellular dehydration causes severe thirst.

Potassium is lost in the urine as the result of tissue catabolism,

secondary to starvation and an inadequate calorie intake, and probably also in association with the mobilisation of cell water for such purposes as insensible loss and urine formation. The severity of the potassium depletion depends on the number and duration of the bouts of vomiting, on the completeness of the starvation and on the extent of the intracellular dehydration. The urinary excretion of potassium is also increased by intravenous administration of isotonic saline and of 5 per cent. glucose solution.

The observations of Cooke *et al* (1952) and of Orloff *et al* (1953) suggest that this alkalosis is confined to the extracellular fluid and is associated with an intracellular acidosis due to the transfer of hydrogen ions into the cells in part replacement of their lost potassium. The composition of the renal tubular cells is presumably affected in the same way as that of the cells of other tissues in the body and in this type of alkalosis will also be more acid than usual. An increased hydrogen ion content of the tubular cells would tend to increase the excretion of acid in the urine and bicarbonate excretion would be diminished. In severe alkalosis associated with potassium depletion the quantity of bicarbonate in the urine is much less than in the glomerular filtrate. The development of potassium deficiency and of severe alkalosis thus depends on several factors At first plasma bicarbonate concentration rises to compensate for the loss of chloride in the vomited gastric juice, later increases are possibly due to the elevated hydrogen ion content of intracellular fluid The kidneys conserve sodium when it is lost in the vomitus, and in the absence of sodium the *p*H of the urine falls The increased cellular destruction to compensate for impaired food intake, and intracellular dehydration following inadequate water intake, lead to the shift of potassium out of the cells into the extracellular fluid, whence potassium is excreted by the kidneys These processes in addition to the loss of potassium in the vomitus, if they continue for long enough, may lead to a large total loss of potassium.

In the early stages of pyloric obstruction there may be little alteration in the composition of the plasma and extracellular fluid. The first indications of the large changes which are occurring in body composition are often an increase in the carbon dioxide combining power and a decrease in chloride concentration

Sodium concentration is maintained by renal conservation and possibly by the mobilisation of sodium from bone. Potassium concentration is maintained by mobilisation from the cells, even when food intake is very small, and falls only when depletion is severe. This is presumably the result of the continued transfer of potassium from the cells because of partial starvation and intracellular dehydration. Even though renal excretion of potassium remains high the reduction of extracellular fluid volume by loss of sodium and water may be associated with an extracellular potassium concentration which is in the upper part of the normal range although a large amount of potassium has been lost from the body. The recognition of these possibilities is important because the frequent finding of a high extracellular potassium concentration has probably caused many clinicians to minimise the importance or deny the existence of severe potassium depletion after prolonged vomiting due to pyloric stenosis. Often when isotonic saline is administered by intravenous infusion the ensuing rapid increase of extracellular fluid volume is accompanied by a marked reduction in the extracellular potassium concentration but not necessarily by any other clinical signs of potassium depletion. When large quantities of gastric secretions are repeatedly lost in a few days, extracellular fluid volume is acutely reduced and the clinical signs of sodium and water depletion appear (see p. 38). This type of acute disturbance is usually successfully treated by the rapid intravenous infusion of isotonic saline. It is important, however, to recognise that the administration of isotonic saline merely increases the volume of the extracellular fluid by providing sodium and water. It does not correct the loss of potassium and water from the cells or repair the ravages of starvation. In gastric juice the concentration of sodium (50 mEq./litre), potassium (10 mEq./litre) and chloride (150 mEq./litre) are unlike those in extracellular fluid (see Table IX, p. 41) After the loss of one litre of such gastric fluid the replacement of the sodium can be achieved with 3 g. of sodium chloride (55 5 mEq), but replacement of the chloride will require 9 g. of sodium chloride (153 mEq.) and of the potassium 1 g. of potassium chloride (13·4 mEq.). The intravenous infusion of a litre of isotonic saline thus provides a large excess of sodium but no potassium, and is an inaccurate means of replacing the lost fluid. The reappearance of chloride in the urine is not an indication of the complete replacement of

chloride, because, as Van Slyke and Evans (1947) showed, the urinary chloride concentration may increase soon after the infusion of saline is started, and may approach the plasma chloride concentration before the chloride deficit is fully replaced

It is only in the later stages of pyloric obstruction, after loss of vomitus has been repeatedly replaced by infusions of isotonic saline, that the effects of repeated losses of potassium become clinically evident with muscular weakness, lethargy, a low serum potassium concentration and a high carbon dioxide combining power

Treatment.—It has been recognised for some years that treatment of severe alkalosis which is based on attempts to lower the high plasma bicarbonate does not always succeed. Indeed, the administration of saline and of ammonium chloride sometimes makes the patients worse rather than better In alkalosis associated with potassium deficiency the correction of the potassium disturbance is of primary importance The administration of potassium salts is known to produce marked improvement in the clinical state of patients with this combined disturbance, even when no attempt is made to correct the alkalosis by administering chloride. Perhaps this is due to the restoration of the intracellular content of potassium which in turn displaces sodium and hydrogen ions from the cells. The intracellular acidosis is thereby reduced and the transfer of hydrogen ion to extracellular fluid diminishes the extracellular alkalosis.

Whenever vomiting has continued for more than a week or ten days, potassium deficiency as well as alkalosis should be suspected. Some indication of potassium deficit may be obtained from change in the general state of the patient, especially recent loss of appetite and energy The serum concentrations of sodium, potassium, chloride and bicarbonate should be measured and an electrocardiographic tracing made

The pre-operative treatment of such a patient is designed to replace the deficit of potassium as well as that of chloride and the smaller loss of sodium. The ideal method is by the oral consumption of as full a diet as can be eaten, combined with the emptying and washing out of the stomach at night a supplement of up to 12 g of potassium chloride per day should be added to the diet. In spite of reducing the daily loss of gastric secretions and increasing the intake of food, fluid and potassium by these

means, there may be a further reduction in the serum-potassium concentration. This is probably caused by an expansion of extracellular fluid volume, which may in part be due to the transfer of sodium from cells to extracellular fluid It is reasonable to continue with this method of replacement if the general condition of the patient improves and the volume of gastric residue diminishes, if not, other methods of replacement must be employed. The institution of a jejunostomy allows of the provision of a full daily intake of calories and protein, together with ample potassium and chloride Alternatively, and in any case if there is coma, extreme drowsiness or persistent vomiting in spite of gastric lavage, the lost water and electrolyte should be replaced by intravenous infusions Before a solution containing a potassium salt is injected, a urine output at the rate of at least 500 ml. per day or 20 ml. per hour should be ensured, if necessary by the infusion of a 5 per cent glucose solution. Up to 2 g (26 8 mEq) of potassium chloride in a 5 per cent glucose solution may be administered over a period of 4 to 5 hours, and up to 12 g. (160 8 mEq) may be given during the first 24 hours Because of the dangers of intravenous administration of potassium, it is wise to change to the oral route as soon as possible

Occasionally, after partial gastrectomy or gastrojejunostomy, the return of gastro-intestinal motility is delayed for more than 48 hours Accumulation of fluid in the stomach and upper jejunum then requires gastric aspiration and the restriction of oral fluid intake Usually this state lasts for at most a few days, but rarely it may persist for a week or more and it then becomes a very serious complication. The cause of this impaired motility is uncertain; depression of the serum-calcium concentration, low plasma-protein concentration, the intravenous administration of excessive quantities of saline and potassium depletion have all been suggested as causal factors. When, because of fear of an organic obstruction, the abdomen is reopened, the stomach and jejunum are usually seen to be immobile and stiff with oedema fluid, the stoma is widely open and across it fluid contents swill to and fro with each respiratory excursion Restriction of the oral fluid intake is not always followed by reduction in the volume of the gastric aspirations The stomach tube should always be withdrawn as soon as the fluid smells clean and is not thickly turbid. Intravenous saline administration should be strictly limited to a

daily quantity sufficient to replace the sodium lost in the aspirated fluid, and the effect of an infusion of potassium chloride should be tried. It is doubtful whether any additional anastomosis should be carried out in the absence of organic obstruction, indeed, reopening of the abdomen and the inspection of the stomach and jejunum alone are often followed by early resumption of normal peristalsis.

LOSS OF INTESTINAL SECRETIONS

High Intestinal Fistula.—Gastric, duodenal, biliary or pancreatic fistulas are rare but highly dangerous complications of operations such as partial gastrectomy for benign or malignant ulcers of the stomach and especially for duodenal ulcer Their recognition is usually made more easily and earlier by drainage of the original operation wound, and this also reduces the extent of the intraperitoneal reaction when leakage begins The daily volume of fluid lost from these fistulas is proportional to the extracellular fluid volume, and is thus directly affected by the degree to which intravenous replacement succeeds in correcting earlier losses of fluid. Some of these fistulas dry up and close after draining for as short a time as 7 to 10 days without particular difficulty being experienced in their management. Others unfortunately persist for much longer periods and cause great anxiety and difficulty in treatment, and from a few so much fluid is lost within a short time that treatment may be unavailing

Duodenal Fistula.—The fluid which is lost from a duodenal fistula consists of a mixture of bile, pancreatic juice and duodenal secretion It is alkaline and contains moderate quantities of chloride, but large quantities of sodium are lost, this leads to reduction of extracellular fluid and plasma volume, haemoconcentration and acidosis Duodenal fistulas most often follow leakage from the duodenal stump after partial gastrectomy They also result when because of extensive ulceration, it is impracticable to dissect the duodenum sufficiently far to permit a closure to be made in these circumstances, drainage of the open end of the duodenum for several days is said to be usually followed by closure of the fistula within a short time after removal of the drainage tube. Such closure possibly depends on the readiness with which the duodenum can empty distally past the gastro-

jejunostomy, and in those cases where there is any interference with emptying persistence of the fistula is common.

Up to 2 litres or more of fluid, containing as much sodium as extracellular fluid, may be lost daily. The replacement of these losses with isotonic saline may restore the sodium and water, but provides an excess of chloride and increases the tendency to acidosis. As the extracellular fluid is depleted by the loss of fluid from the fistula, the volume of the loss declines, but the rate of loss increases soon after the extracellular fluid volume is restored by intravenous infusion. The oral consumption of food and fluids also is soon followed by gushes of bile-stained fluid and undigested food from the fistula. Digestion of the skin round the fistula causes severe pain, but can be prevented by smearing the skin with an alumina paste or barrier cream. (ZnO + Al)

Much of the anxiety and difficulty of treating such a fistula can be avoided by the prompt establishment of a jejunostomy within the first week after the onset of the fistula. The greatest advantage of the jejunostomy is that it allows the collected discharges from the fistula to be run into the jejunum. This prevents the loss from the body of a fluid of complicated composition and there is little if any need for intravenous infusion. In addition, because the full calorie, protein, water and vitamin requirements can be readily supplied by jejunostomy feeding, all oral intake can be stopped and the fistulous losses thereby greatly reduced. The early establishment of the jejunostomy is essential if secondary fluid disturbances due to inaccurate intravenous replacement are to be avoided and malnutrition with impairment of wound healing prevented. Jejunostomy is of limited value when there is an intestinal fistula lower in the small intestine or in the presence of a colostomy.

Biliary Fistula.—A complete biliary fistula may produce severe disturbances in body-fluid equilibrium provided it lasts long enough, the mineral composition of liver bile being very similar to that of extracellular fluid. The illness which may follow prolonged external drainage of all the bile is well recognised, and after deliberate surgical drainage of the common bile duct it is usually avoided by clamping the drainage tube. *Fistula of the common bile duct* occasionally follows inadvertent damage to the duct during dissection of the duodenum in the operation of partial gastrectomy. This type of fistula usually begins to discharge

within a week of the operation, but may cause biliary peritonitis and jaundice before discharging at the laparotomy wound. Specific operative treatment of the fistula is seldom required because most fistulas close spontaneously, but gradual depletion of the extracellular fluid volume may necessitate the intravenous infusion of isotonic saline. The oral intake of potassium should be increased by the consumption of 2 to 4 g of potassium chloride per day for as long as the fistulous discharge exceeds 250 ml per day.

PANCREATIC FISTULA.—Pancreatic juice may be lost from a fistula of an accessory duct or very rarely of the main duct, as the result of injury during operation. An opalescent fluid begins to discharge from the drainage sinus about 48 hours after operation. Pancreatic juice contains sodium, potassium and chloride in concentrations which resemble closely those in extracellular fluid, in the absence of infection the fluid from a pancreatic fistula may contain more sodium than plasma, a difference which appears to be related to the very low protein content of the pancreatic juice. The bicarbonate content varies directly with the secretory activity of the gland and is high after meals The daily output from a pancreatic fistula may vary from less than 100 ml to nearly 2 litres. The pancreatic secretion is unique amongst body fluids in its high bicarbonate content averaging about 80 mEq per litre, the bicarbonate and chloride concentrations vary reciprocally and together equal that of the total plasma anions In a 47 year-old man with a pancreatic fistula Sinclair (1956) found the average daily output to be 880 ml the greatest loss on any day being 1740 ml. a figure which is similar to that recorded from several other patients. *Large acute losses of fluid from a pancreatic fistula may require replacement by intravenous infusion*, when a solution containing a mixture of sodium chloride and sodium lactate should be used and potassium citrate should be administered orally *As long as the general condition of the patient* remains good the fistulous losses can be replaced by drinking a suitable mixture such as fruit juice diluted with half-strength Darrow's solution which Sinclair used. Early recognition of leakage depends very much on the presence of a drain inserted into the neighbourhood of the duodenal stump at the end of the operation.

Acute Intestinal Obstruction.—*For the present purpose*

because of the difference in general metabolic state at the time of onset of the obstruction, intestinal obstruction may be classified into the following two main groups:

1. Acute obstruction or strangulation of bowel in hernial sacs or by bands, volvulus, obstruction by tumours of the wall of the bowel, or acute intussusception.
2. Post-operative obstruction by recent peritoneal adhesion, peritonitis or paralytic ileus

ACUTE PRIMARY OBSTRUCTION OR STRANGULATION.—This causes loss of secretions into the lumen of the bowel above the level of obstruction. The accumulation of intestinal contents above the obstruction stimulates the continued production of secretions and the progress of fluid loss into the intestinal lumen At all levels there is also a loss of fluid into the intestinal wall and the peritoneal cavity The higher the obstruction is in the intestine, the more copious is the production of secretion and the loss of fluid In obstruction high in the intestine, fluid is lost principally by vomiting, and in lower obstructions by simply accumulating in the lumen of the bowel The quantity of fluid lost depends chiefly on the level of the obstruction in the intestine, this is a reflection of the predominantly secretory activity of the jejunum and of the changing emphasis from secretory to absorptive activity down the small intestine and into the colon. Several litres of fluid may be lost by vomiting within 24 hours of the upper jejunum being occluded, whereas the lower colon may be obstructed for 2 or 3 weeks without much loss of fluid, even into the lumen of the large bowel. The addition of a closed loop increases the urgency of surgical relief but does not greatly add to the loss of fluid In strangulation, however, there is a loss of whole blood into the mesentery and the wall as well as into the lumen of the bowel, and when an extensive piece of bowel is involved, this loss of blood is sufficient to cause a large fall in circulating blood volume.

Patients who are admitted in emergency with acute intestinal obstruction do not present straightforward problems in fluid replacement. The urgency of surgical relief of the obstruction often allows of only a short delay for replacement of previous loss of body fluids; survival depends on the choice of the most appropriate fluid to administer before operation. While it is

Wilson (1949) found that, in patients with peritonitis, ileus with large losses of fluid from the bowel was often associated with reduction in plasma volume. A low plasma volume was also found in peritonitis without ileus, and after massive faecal contamination of the peritoneal cavity plasma volume fell steeply before ileus could have had much effect. The likely cause of this reduction seemed to be the loss of plasma by exudation into the peritoneal cavity and the extensive area of inflammation Reduction in plasma volume by 25 to 30 per cent. of normal values was found in half the patients who eventually recovered from severe peritonitis, and in rather more than half of the patients who died The red cell volume of the blood also was reduced in a proportion of patients This fall is usually slow over a number of days and may be due to the loss of cells into the wall and lumen of the inflamed and dilated bowel the loss of red cells may also be due to their involvement in the general catabolism of protein tissue. During ileus the fluid sucked from the stomach often contains altered blood and usually reacts with orthotolidine The inconstant response to large infusions which Theron and Wilson recorded, and the failure in some patients to maintain or increase plasma volume, suggest that another and more complex process than simple fluid depletion may be responsible.

When extensive or generalised peritonitis is encountered, even although the blood volume and peripheral circulation appear to be satisfactory it has been found of value to transfuse the patient with 500 to 1000 ml. of whole blood. Following the transfusion, the needle is withdrawn and the oral consumption of fluid is restricted If the patient vomits, drinking is stopped, and if vomiting is repeated the stomach is aspirated every hour Only very rarely is it necessary to administer fluid by intravenous infusion, and the subsidence of the inflammatory ileus and the reappearance of peristalsis appear to be earlier when the fluid intake is restricted in this way than when large volumes of saline or glucose solution are infused.

In a few patients there appears to be some impairment of vaso-control associated with advanced peritonitis, and even the transfusion of whole blood, plasma or plasma substitutes administration of saline do not make much impression failure, which is the common cause of death. pancreatitis and in biliary peritonitis there

sometimes larger volumes may be necessary, and the volume required by each individual should be judged by the response to treatment. When it has been necessary to restore blood volume before operation it is always wise to continue the intravenous infusion at a slow rate during and for up to 12 hours after operation until stability is certain. Further circulatory impairment is treated by the rapid infusion of dextran or blood. Post-operative saline infusion is of value when large volumes of fluid have been lost before operation, provided that the presence of bowel sounds indicates that there is active intestinal peristalsis Great care must be exercised in judging the volume of saline to be infused, because after operation, especially in a patient depleted by large losses of intestinal fluid, renal conservation leads to the almost complete retention of infused sodium and water. Unfortunately there is no reliable way of estimating or calculating the quantities of sodium and water which should be administered to a particular patient, and it is necessary to judge when to stop by the changes in the appearance of the patient. Restoration of extracellular fluid volume is indicated by a healthy, reddish colour in the skin, which is warm, dry and feels thicker when picked up instead of being pale muddy grey, cold, clammy and shrivelled. The eyes are no longer sunken and dark-ringed, the tongue is moister and not hard, the pulse is slower, full and firm and the blood pressure is within normal limits. As soon as possible the patient should start to drink again and should be fed as soon as he can take food.

POST-OPERATIVE OBSTRUCTION.—After abdominal operations there are three important types of obstruction, or delayed emptying of the bowel, which cause loss of intestinal fluid: first, peritonitis; secondly, kinking or binding down of the bowel by fresh fibrinous adhesions; and thirdly, adynamic or idiopathic ileus in which the bowel appears to have lost temporarily the ability to contract.

In Peritonitis, the intestines which are involved in the intraperitoneal inflammatory process are inflamed and stiff with inflammatory oedema This interferes with peristalsis, and intestinal secretions accumulate in the inflamed bowel and in the intestine above When large quantities of saline are administered to patients with peritonitis, the bulk of the inflammatory exudate is increased and interference with intestinal function is increased and prolonged by the formation of excessive exudate. Theron and

Wilson (1949) found that, in patients with peritonitis, ileus with large losses of fluid from the bowel was often associated with reduction in plasma volume. A low plasma volume was also found in peritonitis without ileus, and after massive faecal contamination of the peritoneal cavity plasma volume fell steeply before ileus could have had much effect. The likely cause of this reduction seemed to be the loss of plasma by exudation into the peritoneal cavity and the extensive area of inflammation Reduction in plasma volume by 25 to 30 per cent. of normal values was found in half the patients who eventually recovered from severe peritonitis, and in rather more than half of the patients who died The red cell volume of the blood also was reduced in a proportion of patients This fall is usually slow over a number of days and may be due to the loss of cells into the wall and lumen of the inflamed and dilated bowel the loss of red cells may also be due to their involvement in the general catabolism of protein tissue. During ileus the fluid sucked from the stomach often contains altered blood and usually reacts with orthotolidine The inconstant response to large infusions which Theron and Wilson recorded, and the failure in some patients to maintain or increase plasma volume, suggest that another and more complex process than simple fluid depletion may be responsible.

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In a few patients there appears to be some impairment of vasomotor control associated with advanced peritonitis, and even the lavish transfusion of whole blood, plasma or plasma substitutes and free administration of saline do not make much impression on the circulatory failure, which is the common cause of death In acute haemorrhagic pancreatitis and in biliary peritonitis there

is often very severe circulatory disturbance, and the peritoneal reaction is due more to chemical than to bacterial irritation Blood volume may be much reduced, but a poor response often follows the administration of blood, plasma or dextran in these two conditions The modern habit of protecting patients from infective complications during the first week or so after operation by the prophylactic administration of antibiotics has resulted in a change in the clinical picture of post-operative peritonitis following intestinal operations. The insidious onset leads almost imperceptibly into a state of severe but indefinite illness; often for several days no more can be said than that the patient does not look well. A sudden fall in peripheral blood pressure may be preceded by some increase in pulse rate. Before exploration or drainage of the peritoneal cavity can be safely undertaken it is usually necessary to prepare such patients by transfusion of blood or dextran.

In Adhesions and Ileus—When abdominal distension is progressive after an intraperitoneal operation, it is of the greatest importance to know whether the accumulation of gas or fluid is due to an organic obstruction, such as a fibrinous adhesion producing kinking or twisting, or to an inability of the bowel to empty itself of contents. Organic obstruction demands urgent release as soon as possible after it has been diagnosed. For true ileus or inability to empty there is no satisfactory or certain relief, and the less such bowel is interfered with the better. Because it occurs in a bowel which is active, organic obstruction causes colicky pain, which is the most important diagnostic feature of this type of obstruction Patients with organic obstruction may have been subjected to gastric aspiration for several days before the diagnosis is made, they may not have complained of pain, or their complaints may have been minimised, ignored or misinterpreted and a copious vomit may be the first sign of intestinal obstruction. Before the obstruction is relieved by operation it is advisable to start an intravenous infusion so that if circulatory failure develops during laparotomy, blood volume can be rapidly increased In some cases it may be wise to start the infusion of dextran before anaesthesia is induced.

After relief of the obstruction the dilated intestine should be emptied of gas and of as much fluid as possible by suction after local puncture with a needle. The emptied loops are then better able to pass on any contents which remain in the rest of the

involved intestine and the abdominal wound is more easily and rapidly closed After operation a careful watch must be kept for signs of impending circulatory failure, gastric aspiration should be continued, but drinking should not be permitted as long as aspiration is continued. As soon as the aspirations become clean-smelling and dark green in colour the tube should be withdrawn and should be replaced only if there is vomiting During the period of aspiration the intravenous infusion may be continued Not more than one litre of 5 per cent. glucose solution should be given each 24 hours If signs of extracellular fluid depletion appear, the rapid infusion of a litre or more of isotonic saline may be required, but potassium salts should not be administered until at least 48 hours have elapsed since operation If the blood pressure falls below normal limits, 500 to 1000 ml. of dextran should be infused rapidly, followed by 1000 to 1500 ml of saline.

Sometimes peristaltic sounds are not heard for 2 or 3 days after operative relief of obstruction, and during this anxious period of waiting for the restoration of peristalsis restraint must be exercised. No good purpose is served by allowing the patient to drink even small quantities of water, thirst is better relieved by frequent mouth washes. Urinary output will be low and it is unwise to attempt to increase its volume by administering large volumes of glucose solution The use of enemata to stimulate the bowel to contract, or of the various drugs which have had temporary vogues in the past, produces inconsistent and uncertain results and often does more harm than good.

Altered motility and muscular inco-ordination of the intestinal musculature may result from severe depletion of potassium or sodium Marriott (1947) suggested that the severe spasms of pain, which are a feature in some patients with advanced pyloric stenosis might be due to sodium depletion Webster *et al* (1950) produced potassium deficiency in rats by feeding them, for periods of at least a month, on a diet deficient in potassium, the rats showed gross disturbances of intestinal motility and distension of the intestines with gas and fluid which responded to potassium therapy When ileus occurs following operation on a gastric or intestinal lesion which has resulted in prior depletion of potassium, it may be due, in part at least, to depressed intestinal motility secondary to potassium deficiency The reduced gastric intestinal motility after prolonged gastric aspiration may have a similar

basis. In such cases the intravenous administration of potassium salts should be tried, success being usually indicated by an early increase in bowel sounds and by the passage of flatus. It should not be forgotten that calcium and magnesium are both liable to be depleted by the same circumstances which lead to the loss of potassium, and that the activity of calcium in extracellular fluid is diminished in alkalosis. Sometimes the intravenous administration of 20 ml. of calcium gluconate has produced a striking if temporary response by initiating peristalsis in patients with ileus. The oral administration of magnesium sulphate has on occasion resulted in the onset of peristalsis and the lasting relief of an ileus.

As soon as peristalsis is once more well established, the patient should be encouraged to drink and eat as full a diet as possible. Sometimes troublesome diarrhoea follows the relief of an obstruction or ileus, and the loss of secretions leads to an unexpected extracellular fluid depletion and to circulatory failure. Any tendency to diarrhoea should be treated by the administration of 10 to 15 minims of tinct. opii and an ounce of kaolin every 6 hours.

Extensive Resection of the Small Intestine.—The evil effects of the wide removal of the small intestine vary widely with the age of the patient. They are most marked in the infant and young child in whom high daily metabolic requirements are supplemented by those of growth. In adults a reasonable existence may be possible after the removal of up to half the small intestine and even greater resections have been survived (Haymond, 1935) Removal of the jejunum is better tolerated than loss of the ileum and is associated with less wastage of nitrogen in the stools (Kremen *et al.*, 1954). Sustained diarrhoea is an important and fairly frequent complication of the removal of more than 30 cm of the terminal ileum combined with total colectomy, the more terminal ileum that can be conserved the less likely is diarrhoea to persist. Besides the loss in a partially digested state of 30 per cent. of the protein intake the continued daily losses of up to 50 per cent. of the fat eaten as well as of water and minerals (both ingested and secreted by the alimentary tract) create a formidable therapeutic problem after a massive intestinal resection and lead to progressive loss of weight, anaemia, protein depletion and oedema. The diarrhoea responds poorly to treatment which, apart from the urgent intravenous replacement of acute losses, depends mainly on supplying readily absorbed food-

stuffs in larger quantities. This is probably one of the few real indications for the oral use of hydrolysed protein, which should be combined with suitable vegetable oils and lactose or glucose. In addition chalk and opium mixture is often of considerable value in delaying the passage of food through the remaining intestine.

Ulcerative Colitis.—The repeated bouts of diarrhoea which are a feature of the acute phases of this disease cause the loss of mucus, purulent discharge, blood and intestinal secretions, as well as interfering with the absorption of the products of digestion of food In addition to malnutrition and the wasting of the body there are losses of water, sodium and potassium in the loose faeces, and severe secondary anaemia. During bouts of diarrhoea it is often necessary to maintain the circulating volume of blood by transfusion of whole blood, and in some cases dextran may be necessary in emergencies to keep the patient alive until blood is cross-matched. The rapid depletion of the extracellular fluid which follows bouts of diarrhoea can be treated successfully by the intravenous infusion of saline and the transfusion of blood only in the early stages Later the progressive loss of potassium requires that potassium salts be added to the diet or to the infusion fluids. Since diarrhoea causes acidosis, Darrow's solution is of more value than saline, and potassium citrate and sodium bicarbonate should be administered orally to supplement the sodium and potassium of the diet.

Ileostomy—During the first 24 or 48 hours after an ileostomy has been established there is usually not much loss of intestinal fluid from the ileum. Subsequently, however there may be repeated gushes of large quantities of thin fluid which occasionally may amount to 3 or 4 litres per day (Warren and McKittrick, 1951 Wilson, 1955) This fluid contains about 100 to 120 mEq per litre of sodium and 60 to 80 mEq per litre of chloride The loss of sodium is disproportionately large and leads to acidosis, and the replacement of the lost sodium by the consumption of sodium chloride results in the ingestion of an excess of chloride. The chloride and sodium contents of the urine are not necessarily related to each other but depend at least in part on the metabolic state and the total body content of these ions. Sodium is the ion of greatest importance in determining extracellular fluid volume, and large unreplaced losses of sodium lead to reduction in extracellular fluid volume. Estimation of the chloride content of the

urine (Fantus, 1936) is of little practical value and is misleading when the loss of sodium exceeds that of chloride.

The losses of sodium and chloride may have to be replaced by the intravenous infusion of saline, or saline and lactate, but sodium chloride and sodium citrate can also be given by mouth. Provided renal function is good and the water intake is adequate, most patients can make satisfactory adjustments for the excessive administration of chloride. In general, it seems best to avoid the routine use of an intravenous infusion after ileostomy and to employ saline infusions only when signs of sodium and water depletion have appeared; treatment must then be thorough and rapid and its accuracy is improved if all the fluid lost from the ileostomy, as well as all urine produced since operation, have been collected and measured, and their sodium, potassium and chloride contents have been measured. If in addition a low-grade intestinal obstruction develops (Counsell and Goligher, 1952) even greater care is needed in the employment of intravenous replacement of lost fluid. It may sometimes be necessary to use dextran in saline to restore circulating blood volume, especially in the presence of intestinal obstruction, but usually the rapid infusion of enough isotonic saline is all that is necessary. The continuing daily loss of potassium in the urine must again be emphasised although more potassium may be lost in the large quantities of mucus (50 to 100 mEq. per litre) in the loose stools. The administration of ACTH or cortisone, and operations such as colectomy, may be other associated causes of loss of potassium.

Diarrhoea may rarely endanger life soon after the opening of a colostomy and, as in ulcerative colitis, much may be done to control the loss of fluid by the oral administration of opium and chalk, or kaolin. The replacement of the lost fluid by intravenous infusion is made more effective if potassium chloride and sodium lactate are combined with sodium chloride in the replacement solution.

BIOCHEMICAL DISTURBANCES AFTER TRANSPLANTATION OF THE URETERS

It has been known for many years that, following the transplantation of both ureters into the colon, acidosis might follow the continuous discharge of all the urine into the lower bowel. It has also long been recognised that subsequent dilatation of the upper urinary

tract, with or without secondary infection, is commonly followed by impairment of renal function. Acidosis may be accompanied by other biochemical changes and the clinical and chemical state of these patients is subject to wide individual variation

The typical biochemical disturbance is an elevation of the plasma chloride concentration, with which is associated a lowered bicarbonate and sometimes a raised sodium concentration, and rarely potassium depletion. This disturbance is found only in continent patients after complete diversion of all their urine to the colon, it may appear at any time after operation, but becomes more common the longer the patient survives and also when renal function is impaired Patients affected in this way are usually easily tired, feel weak and have poor appetites there may be nausea and vomiting, severe thirst and the discharge of large volumes of more watery rectal fluid than is customary The disturbance is often precipitated in a severe form by illnesses such as influenza or by other acute infectious disease. Anuria is rare and is often associated with progressive potassium depletion, the latter may cause flaccid paralysis, severe drowsiness and occasionally coma.

Opinion is divided regarding the primary cause of these disturbances. The most widely accepted explanation is that the acidosis is due to the selective reabsorption of chloride from the urine in the colon. It has also been suggested that the acidosis depends primarily on impairment of distal tubular function resulting from back pressure and hydronephrosis, or from pyelonephritis due to ascending infection Although reflux of bowel contents with back pressure and infection occurs in 50 per cent. of cases after direct anastomosis (Nesbit), but in only 10 per cent. of cases after indirect anastomosis (Coffey or Stiles type) there is little difference in the incidence of acidosis after the two common types of anastomosis (Jacobs and Stirling 1952) The accumulation of urine for four or five hours or more in the colon above a continent anal sphincter seems to be the most important factor common to all cases and this suggests that some alteration in normal colonic function is probably the critical factor This is supported by the rapid and complete relief which is afforded by continuous drainage of the urine from the bowel by an indwelling tube.

The absorption of chloride from the colon depends on the relative concentration of chloride in the bowel fluid and in the plasma. The presence in the lower colon of urine with a high

chloride content makes absorption likely, and the longer the urine is allowed to remain in the colon the greater is the quantity of chloride which may be absorbed. Absorption of chloride in this way interferes with the renal regulation of chloride content of the body even when, as Mitchell and Valk (1953) have shown, renal function is better than the normal minimum. Parsons *et al.* (1952) have confirmed the old observation that when only one ureter was transplanted into an isolated pouch of colon and rectum, the urine from the bladder was strongly acid, whereas that from the pouch of colon was consistently alkaline By adding radioactive chlorine (^{38}Cl) to urine in this pouch they showed that ^{38}Cl concentration rapidly rose in peripheral venous blood and was disproportionately high in the bladder urine. They also showed that ^{38}Cl was absorbed more rapidly than ^{24}Na from urine in the colon. In spite of absorption of sodium from the urine in the bowel, elevation of serum sodium concentration is not common after transplantation of the ureters

The primary disturbance therefore seems to be the absorption of chloride from the urine in the colon. In spite of an increased urinary excretion of chloride in response to this, only part of the reabsorbed chloride leaves the body because some is again re-absorbed from the urine in the colon. Gradually but very slowly there is a tendency for the body content of chloride to increase, but the concentration of chloride in extracellular fluid will vary from time to time according to intake of both chloride and water, and to the frequency of emptying of the bowel. The increased turnover of chloride through the kidneys reduces their capacity to respond to chloride loading, and there is more likelihood of chloride retention through delayed excretion. The renal capacity to respond to variations in chloride intake may be further reduced by functional impairment due to pyelonephritis or hydronephrosis.

The presence of urine in the colon stimulates the secretion of colonic mucus, which is therefore lost in large quantities when the bowel is emptied. The potassium concentration of the mixture of urine and colonic secretion discharged from the rectum is higher than that of the urine alone, and over a period of time significant quantities of potassium are lost from the body. Under normal circumstances, the loss of potassium is replaced by the potassium in the food; when, however, food intake is restricted by illness or loss of appetite, or if potassium excretion is increased

by injury or infection signs of potassium depletion may appear attention was first drawn to this in 1951 by Diefenbach *et al* Thirst is a common symptom in patients whose ureters have been transplanted and suggests that a low-grade chronic intracellular dehydration is fairly common This probably accounts for the inability of these patients to tolerate restriction of their normally high fluid intakes The chief importance of potassium depletion in association with acidosis is the greater mortality and morbidity with which it is associated.

In most patients symptoms are rapidly relieved by continuous drainage of the rectum with an indwelling tube, combined with the consumption of a normal diet. If rectal drainage is maintained for four or five days, the disordered blood chemistry usually returns to normal Intravenous therapy is seldom required except when potassium depletion is severe and there is coma. The disturbance can be prevented by regular emptying of the collected urine from the rectum, at intervals of two or three hours by day, and once or twice during the night. The consumption of up to five or six pints of water per day should be encouraged The intake of sodium chloride should be limited to that used in cooking or preparing the food but it does not seem to be necessary to insist on the provision of a salt free diet. To counteract the tendency to potassium depletion and enhance the effects of restriction of chloride intake, potassium citrate should be administered according to a simple plan for example a stock mixture (30 grains to the ounce) should be taken three times a day for three weeks out of every four and throughout any illness or infection (Wilkinson, 1954)

There is now a tendency, at least in adult patients, to transplant the ureters to an isolated loop of ileum, and also to use ileum as a replacement channel between kidney and bladder when the ureter has been excised. Apart from the elimination of infection, any advantage the use of an isolated loop of ileum has as a substitute for the bladder depends on the loop offering as small an area as possible for the absorption of urinary constituents for as short a time as possible. The loop of ileum must be short and have a wide enough opening on the anterior abdominal wall to allow free escape of urine without delay into a suitable bag Biochemical disturbances may still occur when the loop is too long and the urine is not rapidly discharged from it.

CHAPTER VIII

THE INFLUENCE OF ASSOCIATED DISEASE ON FLUID AND ELECTROLYTE BALANCE

IT is becoming increasingly common for patients with severe disease involving disturbances of cardiac, hepatic and renal function to be submitted to major surgical procedures. As a result more complicated problems in pre-operative and post-operative management have to be overcome, and success may largely depend on the accuracy with which these associated disturbances are recognised and assessed before operative treatment is undertaken Such disturbances mainly affect the control of the volume and composition of extracellular fluid, and in particular the body content of sodium and water; restraint in the use of intravenous infusion therapy is undoubtedly the most important single factor in treatment. This is particularly true in patients who have to be submitted to emergency operation, in whom pre-operative assessment must necessarily be limited. When it is possible to investigate the patient more fully before operation the limits of freedom in treatment can be more accurately defined and greater latitude for post-operative treatment may be secured by suitable pre-operative preparation

CARDIAC DISEASE

It has been recognised for many years that in congestive cardiac disease restriction of the intake of sodium is usually beneficial and that administered sodium is not readily excreted; it is also well known that, provided the sodium intake is controlled, the consumption or intake of water can be maintained at a fairly high daily rate and that some patients respond well to an increased intake of water. In congestive failure renal blood flow is reduced, but an increased resistance in the efferent glomerular blood vessels tends to maintain the volume of glomerular filtrate Nevertheless there may be a reduction in the quantity of sodium filtered by the glomerulus, and in addition increased tubular absorption of filtered sodium may also increase sodium retention.

Moore and his associates (Wilson *et al.*, 1954) have shown how water and sodium retention may increase the morbidity of patients

submitted to mitral valvuloplasty Before operation on non-oedematous patients there were only small increases in the total body content of sodium and water and total potassium was reduced, these changes are in conformity with the wasted state of most of their patients. After operation the usual features of the general metabolic response were seen, but in spite of sodium restriction water retention readily occurred When the sodium intake was not restricted, marked sodium retention resulted and body weight increased This tendency in cardiac patients to exaggeration of the normal post-operative conservation of sodium increases the risk of generalised oedema and its many complications. Although these observations were made on patients submitted to mitral valvuloplasty, they apply equally to other operations on patients with severe cardiac disease The use of local analgesia may reduce some of the hazards of operation in patients with cardiac disease but is unlikely to affect the post-traumatic renal functional changes. The inevitability of these changes and their greater significance in the circumstances of these patients should lead to especial caution in the administration of sodium, and, to a lesser degree, of water, by any routes during the first week after operation

McMurrey *et al* (1955) found that in chronic cardiac invalids with cachexia the blood volume was larger than in health total exchangeable sodium, the extracellular water and plasma volumes being increased as well as the total red cell volume. Their observations afford another reason why transfusion and infusion must be guided with particular care in such patients

The effect of procedures to by pass the circulation through the heart on renal function have been studied by Beall *et al* (1956) During total by-pass with a De Wall-Lillehei apparatus and a blood flow equal to only 25 per cent of normal cardiac output, the renal blood flow and glomerular filtration rates fell to only 25 per cent. of control values, urinary volume fell to a third and sodium and potassium outputs to half the control values. These changes were all due to the reduced blood flow and passed off after the by-pass when blood flow and glomerular filtration rates returned to normal.

Patients with chronic cardiac disease or in failure do not tolerate well a hot environment and their tolerance is further reduced when the humidity also is increased.

LIVER DISEASE

Acute or chronic liver disease may lead to severe disturbances of water and sodium content and equilibrium. The precise way in which these disturbances are brought about remain obscure, but it seems fairly certain that the kidneys are closely concerned. Oliguria or suppression of urine and the delayed onset of a diuresis after the consumption of a large volume of water are well-known features of acute liver disease, and it has long been known that the onset of a diuresis is perhaps the earliest sign of improvement in liver disease of several types. Labby and Hoagland (1947), from studies on patients with acute infective hepatitis, suggested that the normal inactivation of pituitary anti-diuretic factor by the liver may be impaired in severe liver disease, leading to water retention. Their observations may not apply in biliary obstruction until this has lasted long enough to cause parenchymal liver damage. In acute liver disease the retention of both sodium and water by the kidneys presumably is a part of the normal inflammatory response in infective disease; the explanation is uncertain, however, when the liver is damaged by prolonged biliary obstruction in the absence of infection

In cirrhosis of the liver, with or without ascites, there is usually a marked reduction in lean tissue mass and the total body weight is well below the ideal weight Yet at the same time the total body content of sodium is increased and the distribution of body water is altered, the extracellular fraction being unusually high. Protein depletion is usually marked, and with the loss of protein tissue, total body potassium falls. The total quantity of plasma protein in circulation is reduced, but the albumin falls to a greater degree than globulin. The reduction in circulating albumin is another factor leading to distortion of body fluid equilibrium. The factors which lead to the production of ascites are puzzling Ascites may appear after an operation, bleeding from oesophageal varices or during an acute infective illness; in these circumstances it seems to be related not so much to further impairment of liver function by infection, anaesthesia or anoxia as to the renal conservation of sodium and associated retention of water which are part of the general response to operation, haemorrhage or infection. In addition, bleeding from varices is usually followed by a marked reduction in plasma albumin concentration. In patients

with chronic liver disease the daily renal output of sodium remains low in spite of wide variation in the daily sodium intake. Whatever the primary factor in this may be, renal conservation continues with surprisingly little elasticity Over a prolonged period of time it may be possible to strike a balance between sodium intake and output and so to prevent the reaccumulation of ascitic fluid, this balance is precarious and can be upset by slight variations of intake or output, for example, small increases in sodium consumption or minor operations or infections.

Much attention has been given to the depressed plasma albumin concentration which is such a common feature of severe liver disease of all kinds Too little emphasis seems to have been laid on the generalised nature of the protein depletion in severe liver disease. The futility of attempting to increase the plasma protein concentration in a lasting fashion by the intravenous administration of protein of any kind is discussed elsewhere (see p 215) Patients with advanced liver disease often do not tolerate high protein diets, the consumption of a large quantity of carbohydrate ensuring the provision of sufficient calories is of at least as much importance. It is unfortunate that reducing the sodium content of food greatly reduces also its palatability When albumin is administered to an ascitic patient by intravenous infusion, a large part of it is lost into the ascitic fluid, in which the concentration of albumin may increase until it equals that in the plasma. It is interesting that when albumin is injected into the peritoneal cavity some of it may rapidly pass into the plasma

Just as in severe cardiac or renal disease, many patients with advanced or severe hepatic disease are living near the margin of compensation What is sufficient for a quiet life without injury or infection may be too little after operation. Then the chances of survival in all these conditions like the previous maintenance of equilibrium, depend on moderation in all ways. The intravenous administration of glucose solution or saline is particularly hazardous when the normal post-operative renal conservation of sodium is distorted by loss of adaptability and the already sodium loaded state of the body

RENAL DISEASE

The important part which the kidneys take in the regulation of the volume and composition of the body fluids has already been

indicated. So great is the reserve functional capacity of the normal kidney that only in severe or advanced renal disease are the body fluids liable to distortion The large normal reserve allows of great adaptability in function and the main effect of disease is to reduce this elasticity or adaptability. Although an individual with diseased kidneys may be able to live satisfactorily a quiet life, he no longer possesses the means of reacting to the large disturbances of metabolism resulting from a freely chosen diet, violent exercise or severe injury. Because of the impairment of concentration and reduced specificity in absorption and tubular secretion, the formation of an increased volume of urine is necessary for adequate excretion of solutes. Yet the reduced absorptive and concentrating capacity of the diseased kidneys reduces the normal conservation of constituents of the glomerular filtrate, and the unlimited consumption of water, by causing diuresis, may induce additional losses. When in chronic renal disease urinary volume is injudiciously increased, the conservation of sodium may be so far impaired as to lead to reduction of extracellular fluid volume The combination of such sodium loss with the retention of sulphate and phosphate may cause severe acidosis.

The patient with advanced renal disease is a poor subject for a major surgical operation, and his survival may depend largely on whether his remaining renal function is sufficient to deal with the extra excretory burdens imposed by the inevitable post-operative metabolic disturbance. The impaired ability to produce a concentrated urine then demands an increased water intake, but there is also a reduction in the capacity to respond rapidly and completely by diuresis to a sudden large intake of water. If excessive water retention is to be avoided after operation, its administration must be carefully controlled. Especially in elderly patients with impaired renal function, the water intake should not be suddenly increased by intravenous infusion of glucose solution, and the administration of isotonic saline or sodium sulphate solution in an attempt to compel a diuresis is dangerous and ineffective.

Some indication of the severity of the degree of renal functional impairment may be obtained before operation from the examination of the volume and specific gravity of the urine, even in the absence of elevation of the blood urea concentration. For this type of examination to be of any value it is, however, essential

that the urine be collected over short periods of time, not exceeding four hours during the day but the whole of the night urine may be collected in one sample from 10 p.m to 6 a.m. The volume of urine passed in the night specimen is normally only about one quarter of the total and its specific gravity is high, in severe renal disease the nocturnal urine may equal in volume that passed during the remainder of the 24-hour period and be of equally low specific gravity A large volume of urine may also be passed during the night when a large quantity of fluid is drunk late in the evening or when there is urinary tract infection, prostatic enlargement, uncontrolled diabetes or adrenal insufficiency The ability to respond to the ingestion of a pint of water also gives a valuable indication of the functional state of the kidneys, in a *normal* subject there is a prompt diuresis and the specific gravity of the urine falls sharply, but with impaired function there is little change in the volume or specific gravity of the urine.

URAEMIA

The term uraemia indicates an elevation of the concentration of urea in the blood. It is commonly used to indicate the retention in the body of urea produced by metabolism which is a feature of many disturbances of water and electrolyte balance. Urea is an end product of protein metabolism and is not a toxic substance, elevation of its concentration in the blood does not cause harm or give rise to symptoms but may be a useful though unspecific index of alteration in several body functions. A high plasma urea concentration may be an index of impairment of renal function by disease, it may also be due simply to reduced or incomplete excretion, the latter may be the result of osmotic limitation when water for urine formation is insufficient to dissolve all the urea awaiting excretion or because urea formation is increased by tissue catabolism. The term should not be used as a screen for ignorance of the details of the disturbances which determine the survival or death of the patient.

The normal daily output of urea by an adult is about 30 g, and its excretion in the urine results from the selective absorption of glomerular filtrate without urea, the concentration of urea in the urine (2 to 3 g per 100 ml.) being about 100 times that in plasma and glomerular filtrate. Failure to maintain the excretion of urea

may thus be due to reduction in glomerular filtration rate Disturbances of tubular function affect the ability of the kidneys to concentrate the urine, unless the glomerular filtration rate is reduced, however, the quantity of urea which is excreted may not be affected, although its concentration in the urine may fall. Elevation of the blood urea concentration may indicate altered glomerular function, but is not a direct index of tubular function. The urinary urea concentration is a measure of tubular function, since it reveals the concentration in the urine at which the kidneys can excrete urea. The urea clearance test, on the other hand, is an index of glomerular function, since it measures how much of the urea in the plasma at a particular concentration can be filtered and excreted in the urine in a particular period of time, regardless of the concentration at which the urea is present in the urine. Retention of urea is related to impairment of glomerular filtration. Peters and Van Slyke (1931) concluded that urea clearance must be reduced to less than 20 per cent. of normal before patients with impaired renal function exhibit a raised blood urea nitrogen concentration. The blood urea nitrogen concentration can be interpreted correctly, however, only when the rate of urea formation is known. Provided calorie consumption is adequate when their protein intake is sufficiently reduced, many patients with renal disease can maintain their blood urea nitrogen concentration within normal limits In normal subjects excretion of urea usually keeps pace with its formation even after severe injury. Patients with even moderate impairment of renal function may show elevation of the blood urea nitrogen concentration after relatively small increases in urea production.

The clinical state of uraemia is usually considered to be of two types, "renal" or "extra-renal", according to the nature of the underlying disturbance.

Renal Uraemia.—The "renal" type of uraemia is encountered in organic renal disease such as nephritis, or secondary to arteriosclerosis. Its importance in surgical patients is related to the degree of functional impairment which exists and to the consequent loss of elasticity of renal function. The reduced ability of the kidneys to respond to the large metabolic disturbances due to injury and inflammation of all kinds leads to slower and less delicate regulation of the composition of the internal environment.

"*Extra renal*" *uraemia* is due rather to primary disturbances unconnected with the kidneys but which have an effect on renal function. Reduction in glomerular filtration rate may be due to a reduced flow of blood through the kidneys, or to a lowered blood pressure which reduces glomerular filtration pressure. Renal blood flow may be reduced by direct loss of blood or plasma, or by reduction in extracellular fluid volume by vomiting diarrhoea, fistulous discharges or excessive sweating Cardiac disease, especially with cardiac failure, may reduce renal blood flow and is particularly important in elderly patients whose reserve of renal function is low, and in the presence of arteriosclerosis After bleeding into the upper gastro-intestinal tract the blood urea concentration may be raised and then has usually been ascribed to the absorption of products of digestion of the blood in the bowel, in the absence of bleeding, however, the presence of blood in the bowel is not associated with elevation of the blood urea concentration, and it seems likely that alterations in blood urea concentration may be due to effects of blood loss other than digestion and absorption of the shed blood, for example, impaired renal excretion caused by reduction in glomerular filtration rate following severe bleeding (Johnson, 1941)

ANURIA

The term anuria is usually employed when the output of urine from the kidneys is very small or has ceased. Oliguria is usually used to describe reduction in urine volume below 500 ml per day It is probably wise to distinguish clearly between the use of these terms in patients who have lost large volumes of body fluid, because the treatment of anuria due to renal failure is usually incompatible with the replacement of large losses of body fluids

Anuria due to acute renal failure may be caused by

1 Primary renal disease such as acute nephritis or pyelonephritis.

2 Mechanical obstruction in calculous disease of the renal pelvis or ureter in sulphonamide crystalluria or inadvertent bilateral ligation of the ureters.

3 Damage by specific poisons, such as mercury, carbon monoxide or diethylene glycol.

4 Various disturbances such as mismatched blood transfusion

abortion, concealed accidental haemorrhage and other forms of prolonged renal ischaemia.

Oliver *et al.* (1951) described two types of pathological lesion in the kidneys. One type which was found only after poisoning caused necrosis of the cells lining all the proximal tubules, with preservation of the basement membrane, so that regeneration and return of function were possible The other type of lesion affected the whole of the nephron and was patchily distributed through the kidneys; the lining cells and the basement membrane might be disrupted, but not all nephrons were affected, except in a small proportion of cases of massive necrosis. Bull *et al.* (1950) found a uniform pattern of disturbance of renal function in these conditions, characterised by evidence of gross tubular dysfunction and extreme reduction in renal blood flow, and in the fatal cases by a typical pathological picture; they applied the term "acute tubular necrosis" to the whole group instead of that of "lower nephron nephrosis" proposed by Lucké (1946).

The clinical course can be divided into four stages (Bull *et al.*, 1950):

(1) *Stage of onset.*—A period of severe and prolonged shock or diminution in blood flow, or a period during which a toxin such as mercury is acting.

(2) *Stage of anuria or oliguria.*—During this stage, lasting up to three weeks, the renal blood flow falls from the normal of 1200 ml. per minute to as little as 10 to 30 ml. per minute and less than 300 ml. of urine per day is secreted; complete anuria is not common except in cases of massive renal cortical necrosis. Up to half the total deaths occur in this stage, most often from cardiac arrest due to the accumulation in the extracellular fluid of potassium released from the cells. The plasma potassium concentration should be estimated at least once every 24 hours, since it provides a more reliable indication of progress of the biochemical changes than do electrocardiographic tracings.

The accumulation of acid radicles resulting from the catabolism of protein causes a reduction in plasma bicarbonate, leading to a fall in plasma *p*H, stimulation of the respiratory centre and the characteristic deep respiration of acidosis The plasma sodium and chloride concentrations fall, either because of a shift of these ions into cells as a compensation for the outward transfer of potassium or because of dilution by retained water.

(3) *Early diuretic stage*.—This follows in patients who recover with a gradual or occasionally a sudden increase in daily urine output, the volume soon reaching a litre or more but there is at first no evidence of tubular function The duration of this stage is usually about as long as that of oliguria The urine has a low specific gravity of about 1010 and is an almost unmodified ultra filtrate of plasma. Loss of large volumes of this fluid leads to reduction in extracellular fluid volume. It is usually recommended that volume of fluid equivalent to the volume of urine should be added to the daily intake of water Swan and Merrill (1953) have warned against the administration of excessive volumes of fluid during this stage, since they believe that this frequently leads to overloading the body with fluid and thus to prolongation of the diuresis.

(4) *The late diuretic stage*.—It is said that this stage is present when there is evidence of tubular function.

When renal blood flow is diminished in the stage of onset, it affects equally glomerular as well as tubular function. When blood flow is restored, glomerular filtration is gradually resumed, but tubular function is more slowly regained. It is not known how long anoxia must last to produce tubular changes, but undoubtedly the prompt correction of hypotensive states will greatly reduce the incidence of renal disturbances and is the most important way of preventing tubular necrosis. Circulatory disturbances secondary to renal disease may result from excessive loss of sodium and water in the urine or by vomiting, and ultimately give rise to anuria. In all cases of anuria, obstruction of the renal tract must be excluded or treated.

When oliguria occurs at a time when it is not unexpected for example after an operation or accidental injury, diagnosis of tubular necrosis is often delayed. Only when a low urinary output has persisted for several days and does not rise, or perhaps falls further is renal functional impairment suspected In the absence of artificially high intakes of water after operations, oliguria is normal, but the urine is highly concentrated with a specific gravity of 1026 to 1036 Renal failure is not invariably accompanied by oliguria and the passage of pale urine of low specific gravity (1010) may also be an indication of severe renal functional damage. Once suspicion has been aroused, close observation at the bedside and repeated estimation of blood chemical

changes are required. Excessive accumulation of water is shown by haemodilution with a falling packed cell volume or haemoglobin concentration and a fall in plasma sodium concentration. The accumulation of metabolic end-products is indicated by the rising blood urea and plasma potassium concentration. The provision of 100 g. of glucose to an otherwise starving person will reduce the catabolism of protein to a minimum of about 40 g. per day (Gamble, 1947), but the supply of 2000 calories per day and a litre of water may have other effects on metabolism. In the anuric patient the ready availability of abundant carbohydrate may lead to glycogen synthesis and to the removal of some of the excess potassium from the extracellular fluid. The consumption of protein tissue by unavoidable or "continuing" protein metabolism can be reduced to the minimum of about 40 g. per day with the liberation of 6 to 7 g. nitrogen per day only in normal subjects. In patients who have suffered severe injuries, or who have had an abortion with subsequent infection, or whose uterus is undergoing post-partum involution, such reduction in protein metabolism is unlikely. It is usually impossible to predict by how much the blood urea concentration will rise each day, but in such patients the figure will be at least 20 mg. per 100 ml., and may be much higher. After severe injury mean daily rises in blood urea concentration of 50 mg. per 100 ml. have been reported (Teschan *et al.*, 1955; Taylor, 1957). The catabolism of tissue protein may result in the release of nitrogen ranging in quantity from the minimum of 6 g. to 20 or 30 g. per day in the first week after injury. Since 2 to 3 mEq. potassium may be released with each 1 g. of tissue protein nitrogen, from 12 to 60 mEq. potassium may reach the extracellular fluid every day (Tables XVII and XIX). The serum potassium concentration may rise 0·6 to 0·7 mEq. per litre per day after severe injury.

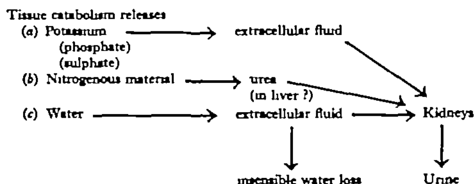
Impaired tubular function in the second and third stages is shown by inability of the kidneys to concentrate urea and creatinine, to conserve sodium and chloride, to extract para-aminohippuric acid from the blood or to reabsorb glucose at a normal rate. There is a rapid initial loss of tubular function, but a very slow return beginning only after several days and becoming complete only after many weeks or months. During the anuric stage there is retention of potassium with the possibility of a toxic concentration being reached, and later, during the diuretic stage,

a risk of a large and prolonged loss of sodium and chloride in addition to a continuing loss of potassium.

Treatment.—The aim of treatment is to keep the patient alive until tubular epithelium regenerates. Any circulatory disturbance causing renal ischaemia must be corrected as rapidly as possible Until glomerular filtration is re-established in the early diuretic stage, water, minerals and other substances cannot be excreted by the kidneys, and if administered in excess of the quantities lost by insensible loss and in the sweat, faeces or vomitus, will accumulate

TABLE XIX

Effects of Tissue Catabolism



in the body Diuretics which act by osmotic effect or on the tubules are useless and may be harmful in the anuric stage, which is also unaffected by spinal or splanchnic block, or by decapsulation of the kidneys.

During the anuric stage water intake must be limited to 1000 ml per day to supply sufficient water for extrarenal losses. Only in this way can water intoxication and extensive oedema be avoided. Similarly, since apart from excretion in the urine the only ways in which sodium and potassium can be lost is by vomiting, in the faeces, or by sweating, there must be restriction of the intake of these elements until diuresis starts Acidosis and alkalosis cannot readily be corrected during the anuric stage and do not appear to influence greatly the prognosis at this time. As Borst (1948) pointed out, uraemic patients seldom eat unless forced to do so, and therefore seldom satisfy their calorie requirements Any protein which they consume will therefore be deaminated and the residues used for energy while the potassium, nonprotein nitrogen

and phosphate which are also released by protein catabolism increase the severity of the bodily disturbance due to failure of renal function.

In the so-called "artificial kidney" the patient's blood is dialysed against a suitable fluid medium across an artificial membrane (cellophane): the composition of the fluid varies with different types of apparatus. The underlying principle of removing substances which are present at an excessive concentration in the plasma and extracellular fluid of the anuric patient can be varied in order to increase or diminish the water content of the body by varying the tonicity of the fluid medium. The development of cheaper and partially expendable apparatus has made the use of this method more widely feasible, but without facilities for careful clinical and accurate biochemical control throughout the 24 hours, the employment of an artificial kidney is not justified. There is no doubt that lives have been saved with this procedure, but successful use of the apparatus demands that a skilled and interested staff should be available at all times.

The number of patients who require dialysis is not large and success with this type of treatment depends on sufficient skill and facility being acquired by the team who work the apparatus and control the treatment; there is a place for only a limited number of units of this kind in any country if satisfactory standards are to be achieved. Of all the patients treated in this way perhaps more than half will die The use of some form of "artificial kidney" is probably indicated when the serum potassium concentration exceeds 7 mEq. per litre in spite of more conservative measures to reduce it. Very severe acidosis with a serum bicarbonate level below 10 mEq. per litre may also be an indication, but there is some question whether the blood urea concentration is a satisfactory index in spite of its implication of the retention of a variety of products of metabolism The rate of deterioration in the whole clinical picture is probably the best basis on which to decide, particularly the onset and deepening of coma, hiccough and twitchings. An "artificial kidney" is likely to be of most use in previously healthy patients whose renal failure follows severe injury, infection or an obstetric mishap.

Catabolism of tissue protein can be reduced without much increase in the sodium and potassium content of the body by feeding a suitable mixture of fat and carbohydrate; Folin (1905)

50 g. of glucose (Bywaters and Joekes, 1948), which causes deposition of potassium in glycogen. Potassium may be extracted from the body with an "artificial kidney" or by peritoneal dialysis These methods involve a great deal of additional interference with a gravely ill patient and the provision of special apparatus, and introduce extra problems in the maintenance of fluid balance. Elkinton *et al.* (1950) suggested that potassium might be extracted by a carboxylic ion exchange resin charged with ammonium and administered orally and by enema. The exchange of sodium and potassium ions from the gastro-intestinal secretions for the ammonium or hydrogen ion of the resin depends on several factors such as the *p*H of the medium or fluid in the intestine, the amount of resin employed and its binding capacity, the total quantities and the proportions of sodium and potassium as well as other cations such as calcium and magnesium in the medium and the time the resin remains in the bowel. The theoretical binding capacity of a resin is seldom fully satisfied and is modified by other factors such as the presence of antibiotics. Perhaps their greatest disadvantage is their lack of specificity in removing any available cation and so a proportion of the available sodium as well as of potassium, will be extracted, this sodium depletion may increase the difficulty of management of anuric patients and conversely in other kinds of renal failure with sodium retention the extraction of potassium may be undesirable. Evans *et al.* (1953) have since recommended that a sulphonic resin charged with sodium, which produces a more rapid exchange and avoids the use of ammonium, is more innocuous and has considerable theoretical advantages in anuria. The small amount of sodium which is given up by this resin does not cause oedema or hypertension. In anuric patients the high blood urea may be further increased by a resin charged with ammonium, and exchange may be limited by the already high urea concentration of the colonic contents The resin is administered in doses of 15 g, in water or mixed with syrup, three or four times a day, or 30 g daily by enema. In addition, a fat-glucose emulsion should be administered by mouth or 50 per cent solution of glucose should be administered by intravenous infusion The disadvantage of administration of a resin by enema is that the uptake of potassium by the resin is related to the length of time the enema is retained, and unless this is for 12 hours or more, little exchange occurs.

More potassium is exchanged when the resin is given by mouth but many patients are nauseated, and lose their appetite or vomit the resin while others become constipated or may have diarrhoea, occasionally there may be delay in gastric emptying or intestinal ileus which both limit exchange. In some cases Evans *et al* (1953) found that the resin extracted 25 to 75 mEq potassium per day, which is a good deal more than is being released from the cells, except at the peak time during the first 72 hours after injury They recommend that the resin should be given as soon as the serum potassium concentration exceeds 6 mEq per litre (23·4 mg per 100 ml) and be continued until it falls below 5 mEq per litre (19·5 mg per 100 ml)

During the last 10 years there has been a marked increase in the number of anuric patients who have recovered. This improvement in the results of treatment deserves some further examination. The careful restriction of the intake of water and minerals which has received much emphasis in recent forms of treatment is in marked contrast to earlier attempts often prolonged for several days, to induce a diuresis at all costs by the infusion of solutions of sodium sulphate or glucose. The descriptions of the clinical course and manner of death of patients treated by these infusions strongly suggested that they died of pulmonary oedema or water retention. It is difficult to judge how much of the recent improvement in results is due to the administration of a large daily supply of energy as glucose or fat. It is conceivable that equally good results might be obtained much more simply by careful restriction of water and mineral intake, coupled with the administration of only 100 g of glucose or lactose per day and the removal of extracellular potassium with a resin. It should not be forgotten that after surgical operations or accidental injury the post traumatic protein catabolism cannot be prevented by the provision of large quantities of energy as fat or glucose, and that similar protein catabolism follows abortion and other obstetrical causes of anuria. In anuria caused by primary renal disease, poisoning or obstruction of various kinds, the accumulation of products of tissue catabolism largely results from starvation, in these circumstances it is likely that protein catabolism can be reduced to a minimum and ketosis abolished by the daily consumption of only 100 g of carbohydrate.

Most patients with anuria will be receiving injections of an

antibiotic and may have been given a sulphonamide drug. Sulphonamides must be stopped. Crystalline penicillin may safely be given in a daily dose of up to one mega unit. Streptomycin, chloramphenicol, aureomycin and terramycin, however, will soon cause toxic effects if their administration is continued, and a single dose will be sufficient to maintain an adequate concentration during the anuric stage.

It is usually recommended that during the diuretic phase sufficient water to equal urinary volume is added to the basal 1000 ml of water intake. If this advice is followed an artificial and entirely undesirable diuresis may be induced, a diuresis which often becomes larger day by day, and which in association with some persisting impairment of renal tubular function may cause large unnecessary losses of sodium and potassium. For this reason it is better and safer to maintain a mild state of dehydration or water lack until renal function recovers more completely. Because of the rapid loss of potassium in the urine, potassium should be supplied in the form of fruit and fruit drinks, and if the serum concentration falls, as potassium chloride by mouth up to 6 g. per day. The body content of sodium and chloride is similarly maintained by supplementary intake of sodium chloride, as indicated by daily measurement of the serum-sodium and chloride concentration, and if possible by measurement of the urinary output of sodium and chloride.

Recently attempts have been made to reduce protein catabolism in anuric patients by administering testosterone or one of its derivatives. Even in normal subjects the effect of androgenic hormones on protein metabolism is small and transient and the use of these hormones in women and children is limited by their virilising effects. The work so far reported on chronic and subacute renal failure has some encouraging features (Gjorup and Thaysen, 1958), but there is less reason for optimism in the severe acute disturbances of renal failure associated with extensive burns and other injuries.

CHAPTER IX

DIAGNOSIS

AN accurate and detailed history of the illness is the most important factor in the diagnosis of fluid and electrolyte disturbances There must be careful inquiry into the consumption of food and fluids as well as into the losses by vomiting or diarrhoea, for on the disparity between intake and loss depends the justified suspicion of water and ionic disturbances which leads to specific investigation. The severity and duration of loss of weight, especially when combined with the best previous weight and the ideal weight for the height, sex and age of the patient, are of particular importance in judging the significance of fluid losses The physical condition and sometimes the mental state also, provide further evidence of the effects of fluid depletion, the effects of loss of water (p 18) sodium (p 35) and potassium (p 55) have already been described in obese people some of these clinical appearances may be obscured by fat. The proper partition of weight loss, and the assessment of the proportions caused by fat catabolism in partial starvation or by fluid losses and protein catabolism, is uncertain and difficult, particularly in fat people.

All patients should be weighed on admission, if an accurate stretcher type of weighing machine is available, frequent, even daily weighing provides valuable information regarding the summated effects of fluid losses and therapy A normal adult whose intake of water and food has been stopped will lose weight at a slowly declining rate, initially in a temperate environment water loss and tissue catabolism will amount to about 1 5 kg per day When water is freely supplied the daily weight loss diminishes to about 500 g per day A patient who is losing large volumes of fluid by gastric aspiration or diarrhoea loses weight more rapidly than if he were only starving conversely when a fluid loss is replaced, its retention in the body offsets weight loss Although a patient may thus gain weight, this does not give any indication of the location of the added fluid which instead of reaching the interior of the cells as was hoped, may instead be accumulating as oedema fluid in the lung bases or in the buttocks. Failure to lose weight or an unexpected gain in weight is an indication to search for oedema. Although a steady loss of weight

may be due to normal consumption of tissue and loss of body water in starvation, it may also be due to the failure to replace losses adequately. There cannot be fixed rules for the interpretation of changes in body weight which must be regarded rather with intelligent curiosity.

Apart from the common ground of good history-taking and clinical examination, the degree of diagnostic accuracy and refinement which is possible in any particular unit depends to some extent on the accurate collection and recording of the urinary output and fluid losses by vomiting, fistulous discharges or faeces, and in part on the biochemical facilities available for the examination of blood and other fluids. The most important factor is, however, the use which is made of the information thus obtained. The possible effects of change in bodily composition are endless. It is essential, therefore, to try to follow some simple plan by which the important and lethal disturbances receive first attention in recognition and treatment The evidence which is obtained from the type of scheme shown in Table XXI (p. 188) enables some estimate to be made of the total quantity of abnormal fluid losses and of the interference with normal intake of food and water; from this a rough approximation can be reached of the potential loss of such constituents as potassium, sodium, chloride and water.

A hypothetical example of the kind of information which can be obtained by calculation when the patient's height, sex, age and the recent changes in body weight are known is shown below.

TABLE XX

Total body weight		*Fat*	*Fat-free weight*	*Total Body Water*	
				60% of ideal wt	*70% fat-free wt*
lb	kg	kg	kg	litres	litres
168	76 3	24 99	51 3		35 91
154	70 0	20 71	49 29		34·5
140	63 4	16·22	47 18	38 04	33 02
98	44 4	5 19	39 21		27 44

A man aged 45 years, height 5 ft 6. in. (157 1 cm.), who suffered from duodenal ulcer with pyloric stenosis, weighed 11 stones (154 lb., 70 kg.) at the onset of a prolonged series of

bouts of vomiting which lasted 9 weeks At the time of admission he weighed 7 stones (98 lb, 44 4 kg) The best weight he had ever achieved was 12 stones (168 lb, 76 3 kg), and the ideal weight for a man of his height and age is 10 stones (140 lb, 63 4 kg) By using the formula of Allen *et al* (1956) (p 6), the fat content of this man at the various weights can be calculated and then the information shown in Table XX can be obtained. The estimate of total body water based on ideal weight is a good deal higher than those based on fat free weight. From these calculations the total loss of weight 56 lb (25 6 kg) can be divided into 34 lb (15 5 kg) of fat, 15 5 lb (7 06 litres) of water and a remainder of 6 6 lb (3·02 kg) of tissue solids

There are several ways in which such estimates of the fractions making up lost weight can be interpreted, and the best choice depends on obtaining a sufficiently detailed history of the illness. A chronic loss in which starvation is an important factor produces a set of changes which are more likely to reflect the findings of McMurrey *et al.* (1955), with only small reductions in the extracellular fluid volume and sodium content but large reductions in the volume of intracellular fluid and the body content of potassium. These changes are also likely when the loss of weight is associated with prolonged diarrhoea as in ulcerative colitis or neglected malignant disease of the colon or rectum. The more acute the disturbance, the more likely are reductions in sodium content and the volume of the extracellular fluid and the smaller is the fraction of the total weight loss which can be safely ascribed to the catabolism of storage fat. Fortunately in acute disturbances depletion of the extracellular fluid is usually readily recognised and promptly treated. In the hypothetical case which has been described there was a loss of 7 litres of body water, and if the reduction in extracellular fluid volume is of the order of only 10 per cent. (1 litre) of the original volume of 9 to 10 litres the remaining 6 litres can be attributed to intracellular water This quantity would contain 660 to 700 mEq of potassium, and if there has been disproportionate loss of potassium from the body the potassium deficit may be even larger

It should always be the main object of the clinician to make an accurate diagnosis from the history and physical examination of the patient, and to resort to the chemical examination of the blood only for confirmation of that diagnosis. In some patients a

CHAPTER X

TREATMENT

GENERAL PRINCIPLES

WHEN there has been loss of body fluid, the objectives of treatment are three:

1. To ensure survival by maintaining an adequate volume of blood in active circulation.
2. To stop the loss of fluid.
3. To repair the damaged and distorted body fluid pattern by the administration of an appropriate combination of water and electrolyte.

Success in treatment depends on the individual consideration and management of each patient and on gaining and keeping control of the fluid and electrolytic balance of the patient. The first step is to make an assessment of the present state of the patient, and then to try to estimate the rate and direction of progression of the disturbance and so to decide the measures which must be adopted.

The duration and severity of fluid loss can be judged from the history and clinical appearance of the patient. Signs of circulatory impairment are of first importance; those of loss of water or wasting of tissues, although notable, are not of immediate therapeutic concern. Body weight may give an indication of the total water state of the body, and the volume and composition of the urine may show how renal mechanisms have compensated for losses of body fluid. Changes in the serum concentration of sodium, potassium, chloride and bicarbonate will show what alterations have occurred in the composition of the extracellular fluid, and may give indirect evidence of changes in intracellular fluid, but the volume specific gravity and concentrations of sodium and potassium in the urine may give even more useful indications. The haematocrit or packed cell volume indicates the presence and degree of dilution or concentration of the blood. The response to treatment also is judged by the changes in the clinical state of the patient, by repeated estimations of serum-electrolyte

concentrations, blood pressure, pulse rate and peripheral skin circulation, volume, specific gravity and composition of the urine, and, if possible, by repeated weighing of the patient.

The cellular environment depends primarily on the maintenance of an adequate circulating blood volume, transfusion of blood plasma or a plasma substitute is therefore the first measure to be considered in all cases. Replacement of deficits of water and electrolyte is important, but in many surgical emergencies it is a secondary consideration, provided blood volume is maintained. In diseases for which operative relief is less urgent, attention may be given to replacement of electrolyte deficiencies, but it should be recognised that time is required for the normal distribution of administered water and electrolyte in the body, and that whereas sodium deficiencies can be replaced in two or three days, at least a week or more may be necessary for the slower process of potassium assimilation by the cells.

In designing any required combination of fluids for complete intravenous maintenance, care must be taken that provision is made for the secondary changes of acidosis or alkalosis, and that the replacement fluids do not themselves create further biochemical disturbances. In addition, water to cover the daily insensible loss and for urine formation, and 100 g of glucose daily to prevent ketosis and reduce tissue catabolism, must be provided. The complete and accurate intravenous replacement of lost body fluids is impossible, and the best approximations to this ideal inevitably omit some of the constituents of the lost fluid, when intravenous replacement is continued for a long period, secondary disturbances, due to the inaccuracies in the replacement fluids, are almost unavoidable.

Prevention is better than cure and reduces the difficulties of compounding suitable mixtures of minerals for intravenous administration If possible, therefore, losses should be reduced by curtailing the oral intake of food and diminishing intestinal activity with opium, and when direct surgical attack on the lesion causing the loss is not feasible, fluid lost by gastric aspiration or from biliary duodenal or pancreatic fistulas should be collected and returned to the alimentary tract at a lower level through a jejunostomy The opposite procedure may be required, for example in ulcerative colitis when the alimentary contents are diverted from the irritated colon by an ileostomy, or in the treat-

ment by rectal drainage of acidosis following transplanation of the ureters.

Fluids injected into the blood stream are beyond the control of the administrator as soon as they leave the needle, and their fate and effects then depend on the conditions within the body. The only components of blood which will remain to any large extent within the vessels are the red blood corpuscles. Albumin is normally retained by the walls of peripheral capillaries, but freely traverses the capillary membrane in viscera such as the liver. After injury and during inflammation, in the affected areas even the peripheral capillaries are freely permeable to albumin and globulin. Crystalloid and glucose solutions rapidly leave normal capillaries until a new equilibrium is established in the extra-cellular fluid; in the absence of any loss by diuresis this would imply the transfer of up to 75 per cent. of such solutions to the interstitial fluid within about two hours of their infusion.

PRE- AND POST-OPERATIVE TREATMENT

Most patients are in good condition when admitted to hospital and do not require any special preparation for operative treatment. A small number have lost body fluids or are suffering from malnutrition, anaemia or other disturbances which increase the risk of subsequent complications. An accurate and detailed history of their illness and a careful clinical examination usually enable this minority to be readily recognised.

In the average uncomplicated patient, it is usual to maintain a normal intake of food and fluid until about 24 hours before operation and then to provide a lighter diet for the last three meals. Even on the day of operation some fluid should be provided in the early morning, although the quantities should be strictly limited in view of the inhibitory effect of pre-operative nervousness on gastric function. After all major operations there is a loss of appetite lasting in varying degree for 2 to 4 days and it is unusual for even light food to be taken for 48 hours. Thirst is usually very severe and is relieved only transiently by drinking and not at all by intravenous infusion of glucose solution or saline

There is a welcome tendency to return to the older mode of

post-operative treatment, in that apart from maintenance of blood volume by blood transfusion, fewer and shorter routine intravenous infusions are being used After operations on the alimentary tract, gastric aspiration is being used more as a necessity when there is an accumulation of gastric secretion than as a routine measure in all cases Although post-operative treatment varies very greatly in different clinics, the results of different kinds of treatment are so similar that it is likely that the good results are achieved in spite of much of the treatment that is provided. The sooner the patient resumes the consumption of food and is able to return to a full diet the better, and any treatment which delays this should be avoided as far as possible.

After all major operations it is desirable to record the intake and output of water The value of such records varies directly with the interest shown in them by the medical staff, the charts must be checked and the use made of the information thus collected must be made evident to the nursing staff Inaccurate routine fluid records are dangerously misleading and may be worse than none. Not only must the record for each 24-hour period be examined but a cumulative total must be kept of output and intake and once a day these totals should be carefully examined and treatment modified according to the information thus obtained. It is obvious that control of replacement will be much more accurate if it is possible for the chemical composition of urine and aspiration or discharges to be measured before the daily decision is made about the mineral and water requirements, measurements of this kind are of much more value than those of the serum concentrations which indicate only the temporary endpoints of extracellular concentrations after the compensatory reactions stimulated by the fluid losses have corrected the original disturbance. To reduce the burden on the nursing staff, fluid records should be maintained only for the minimum essential period. To many surgeons their main value lies in the record of urine volume which they provide. If the specific gravity is also measured an excellent crude indication of renal function is provided. For several days after major operations it is normal for the urinary volume to be between 500 and 1000 ml. and its specific gravity to exceed 1026 Abnormal renal function is indicated by a low specific gravity combined with oliguria or by unusually severe or prolonged oliguria In seeking a cause for such urinary

variation, extra loss of water by vomiting, gastric aspiration, fistula or diarrhoea, inadequate intake, or renal disease or failure should be considered.

The ability of the body to recover from severe accidental or surgical injury has been underestimated for too long. It is exceptional for patients to require the intravenous or other administration of fluid after uncomplicated operations The introduction of the continuous-drip intravenous infusion about 25 years ago gradually led to its indiscriminate use, with little regard to its adverse effects. Only when loss of body fluid causes a significant reduction in extracellular fluid volume, with obvious changes in appearance or reduction in blood pressure, is replacement necessary for survival Intravenous infusions should therefore seldom be necessary even after operations on the alimentary tract.

Many surgeons as a matter of routine arrange for an intravenous drip infusion to be maintained during and after all major operations. This unnatural state of fluid "balance" does not cause ill effects so long as the volume of fluid which is administered is carefully controlled , but the procedure causes additional discomfort and anxiety for the patient and is probably biologically unsound

After injury, renal function is altered but is very rarely impaired and renal damage due to severe injury is extremely uncommon. Oliguria is the natural response to injury in a well-functioning organism, and so is a large excretion of potassium in the first 48 hours, and of nitrogen for a week after injury; the close conservation of sodium and chloride is the equally natural obverse of the survival process. Therefore it seems important to emphasise that, after operation, before fluid losses are replaced, their volume and if possible their electrolyte components should be accurately measured and a judgment made of the possible harm the loss will do if not replaced It may then be decided that replacement of all or some of the constituents is advisable. The volume, composition and rate of administration must be carefully controlled The fluid should be drunk if possible. The dangers of administering excessive quantities of fluid by intravenous infusion are well and widely recognised, but it does not seem to be so well appreciated that the subcutaneous and rectal infusion of fluid is just as dangerous as intravenous infusion, and often as uncom-

fortable and even more distasteful These methods also lack the certainty of intravenous infusion.

The routine use of a prophylactic intravenous infusion during operation makes the transfusion of blood or plasma substitutes too convenient. So much is done to patients nowadays that every reasonable reduction in the number of procedures should be made. Whole blood is a potentially dangerous as well as a precious fluid and should not be lightly used The practice of routinely infusing 5 pints of fluid (4 of glucose, 1 of saline) in each 24 hour period for 1 or 2 days after major operations such as gastrectomy colectomy or excision of the rectum lacks precision and is an orthodox routine unrelated to the actual requirements of the patient. In the absence of severe bleeding, or large or repeated loss of intestinal secretions, such patients do not need blood transfusions or intravenous infusions, and provided they have been properly prepared for operation, are capable of surviving in good condition without a water intake until, after 24 or 48 hours, they are able to drink. Such routine post-operative infusions probably satisfy an urge for therapeutic activity and do not do much harm, but they do not diminish thirst or prevent eventual loss of weight and have not been shown to promote recovery (Wilkinson, 1956 b) They increase the risk of complications such as chemical phlebitis, and of water intoxication or sodium retention if errors are made in the administration, they may delay the return of normal gastro-intestinal motility and certainly lead to undesirable restrictions of movement.

If fluid is administered by intravenous infusion, the total quantity should be limited to something near the daily requirements of up to 1 litre for insensible water loss and 500 to 700 ml. for urine formation. Not more than 2 litres of glucose solution per day should be given, and most patients do better with less than this It is uncommon for the urine output to rise much above a litre per day in the first week after operation The post-operative urinary loss of potassium cannot be stopped and usually lasts for only 48 to 72 hours It will be replaced when food is again consumed, and its routine parenteral replacement is not indicated A few recent reports have advised that up to 80 mEq potassium (6·0 g potassium chloride) should be administered per day to patients who are receiving intravenous infusions, within 48 hours after operation the administered potassium will be excreted in

the urine, and because of oliguria its administration is dangerous and unwise; after 48 hours potassium salts should be administered only if some deficiency existed before operation and if repeated gastric aspiration must be continued, or if there are other losses of body fluid.

The number of patients who need specific replacement therapy before operation is small In these few patients sufficient time must be allowed for the administration of adequate quantities of water and appropriate ions, and for the subsequent adjustment of equilibrium within the body before the operative injury is inflicted. In emergency, when operative treatment can be delayed only for an hour or two, the restoration of deficient circulating blood volume is all that should be attempted. In patients who have been losing fluids or partially starving for several weeks, even a week or two may be too short a period over which to attempt to correct the resulting disturbances in bodily composition, some of which may be finally overcome only late in convalescence after operative treatment In these patients, some compromise or balance must be reached between the restorative treatment of the general bodily disturbance by intravenous and other types of replacement therapy, and the operative surgical attack on the causal lesion. Severe protein depletion by partial or complete starvation leads to impaired wound healing and disruption of intestinal anastomoses It is arguable that time spent on improving protein and general nutrition is worth a delayed operation and the possible extension of the primary disease, if post-operative recovery is to be smoother and more certain

The importance of improving the nutrition of surgical patients as well as the difficulty in doing so are now more widely recognised. The advantages of attacking formidable disease processes by stage operations have long been recognised and accepted; a similar stage-by-stage approach to the severe and sometimes complicated chemical disturbances in surgical patients also deserves wider application. The use of an ileostomy in ulcerative colitis as a preliminary step to colectomy has the double advantage of diverting the faeces from the colon and of reducing the irritation of the diseased colon and thus the loss of blood, purulent exudate and intestinal secretion. As has already been shown, patients with intractable pyloric obstruction may lose by starvation and vomiting up to 40 per cent. of their initial weight

Although part of this loss is made up of catabolised fat, the larger part consists of water and protein tissue, with considerable associated losses of potassium and sodium. The sodium and part of the water losses can be made up rapidly by the intravenous infusion of saline. Part of the potassium depletion also can be corrected fairly rapidly, though still more slowly than is the case with sodium, simply by the intravenous and oral administration of potassium chloride, the remainder is only slowly restored and perhaps depends to some extent on the reformation of previously catabolised protein tissue. Unless the consumption of food and an adequate daily intake of energy are resumed, correction of potassium depletion is incomplete and there is a variable liability to recurrence or the appearance of the clinical disturbances due to potassium deficiency after operative treatment of the pyloric obstruction In severe cases even gastro-enterostomy should be postponed until nutrition has been improved and potassium depletion fully corrected by two or three weeks of jejunostomy feeding

RESTORATION AND MAINTENANCE OF BLOOD VOLUME

Acute reduction of circulating blood volume follows severe bleeding due to accidental injury or surgical operation and is best corrected by the rapid transfusion of an equal volume of blood, or dextran Provided such pre-operative replacement is early and adequate, it should not be necessary to transfuse additional blood unless bleeding recurs or is continuous Plasma loss in burns should also be rapidly replaced by dextran, but because of the continued loss of plasma for up to 40 hours after injury, further infusions may sometimes be required after extensive injuries. After loss of small volumes of blood of up to 1 litre, dextran may be used instead of blood, but blood is of value in extensive deep burns in which there has been destruction of whole blood. Blood volume may be acutely reduced by the rapid loss of intestinal secretions in acute intestinal obstruction. This is best treated by the rapid infusion of dextran, saline also is of value especially after surgical relief of the obstruction.

Chronic reduction of circulating blood volume follows the repeated loss day after day, for weeks or months of small quantities

of blood, for example from a gastric or caecal carcinoma or from bleeding haemorrhoids In severe chronic anaemia great care must be exercised during the transfusion of blood, or any other fluid, because although circulating blood volume may be only 2 litres, the blood pressure is within normal limits (McMichael *et al*, 1943); Sharpey-Schafer (1944) showed that there is, under these circumstances, increased cardiac output which depends on an elevation of right auricular and venous pressures, a type of compensatory "heart failure" which is liable to cause acute pulmonary oedema or auricular dilatation when the circulation is further overloaded by transfusion. This disaster can be avoided by the repeated slow transfusion of small volumes of blood or packed cells and by the close observation of the state of the neck veins of the patient. Severe anaemia should be treated by transfusion until the haemoglobin concentration reaches 10 4 g. per 100 ml. (70 per cent. Haldane) Such transfusions should be completed several days before operation so that reactions do not occur on, or just after, the day of operation.

Although transfusion of whole blood is undoubtedly beneficial to patients who are malnourished and anaemic, the duration of some of the good effects of transfusion is limited In a protein-deficient patient the protein of the administered red cells and plasma becomes part of the common protein "pool" of the body, and may be used simply as a source of protein components. Correction of anaemia by transfusion of whole blood or packed cells thus has only a temporary effect, lasting as long as it takes the body to utilise about 80 per cent. of the injected protein.

Up to 30 per cent. of any population predominantly of Indo-European or African stock is Rhesus negative and about half of these will be sensitised and develop Rhesus antigen if they are transfused with Rhesus positive blood If a Rhesus sensitive female conceives a Rhesus positive child its antigen will react with the mother's antigen and a severe reaction will result. It follows that the more frequently transfusion is employed the greater is the risk of all kinds of reaction and of sensitisation of the recipients to other though rarer and weaker antigens than the Rhesus type; the use of blood transfusion must be restricted to those occasions when it is essential Good organisation and the public-spirited attitude of voluntary donors have made blood transfusion too easy and the use of blood is often uncritical and too lavish

PLASMA SUBSTITUTES

A plasma substitute is a preparation of a colloid such as gum acacia or dextran which is designed to replace human plasma or serum in the treatment of low blood volume states, such as that in shock due to the loss of blood or plasma.

The term plasma substitute is only one of a number which have been employed for these preparations. They are substitutes for plasma only in the sense that they are expected to occupy an equal space within the vascular system. Both gum acacia and dextran are carbohydrates with complicated molecular structures and neither contains any protein. The best alternative term is blood volume expander, but this also is not entirely accurate, since it is the plasma, or non-cellular fraction of the blood volume, which they are designed to increase. Plasma substitutes are necessary, first, when the available supplies of blood and plasma are insufficient to meet the existing requirements, and secondly to provide a stored reserve in readiness for use in future large-scale emergencies. In addition, they are of value in some countries where transfusion services do not exist or where donors are scarce because of the fear of losing ' vital force by giving blood and the maintenance of steady supplies of blood is difficult, in these circumstances plasma substitutes provide valuable alternative agents to whole blood and its derivatives.

An effective plasma substitute must have certain properties. In solution its viscosity should resemble that of plasma and it should exert an osmotic pressure similar to that of the plasma proteins It must be stable for long periods over a wide range of temperature. It must be easily sterilised but free of pyrogens, and yet be capable of cheap manufacture in a constant form. When injected in therapeutic quantities it must not be toxic or antigenic, although being retained in the blood stream long enough and at a sufficiently great concentration to cause a lasting increase in blood volume, the material should also ultimately be completely excreted from or metabolised in the body

The purpose of a plasma substitute is to increase in a lasting fashion the volume of fluid in active circulation within the blood vessels. The success of a particular preparation in thus occupying space within the vessels depends on how completely its molecules, with their associated molecules of water are retained within the

capillaries. This retention depends on the physical properties of the substance, and in particular on the size and shape of its molecules. Size is probably the more important factor, but at certain critical points shape may determine whether the molecules of different substances, but of the same weight, will pass through the capillary wall. It has been suggested that molecules of substances used as plasma substitutes may adhere together in loose aggregations; these aggregations may then produce unexpected physcial effects on blood pressure which are not easily explained. It is also possible that some of the effects of these substances may be due to their molecules adhering to plasma protein molecules.

It has been assumed that most of the osmotic effect of plasma is due to the plasma albumin (Scatchard, 1952) and that the efficiency of plasma substitutes is similar in plasma and in solutions of albumin. The molecular weight of the plasma proteins varies from albumin 69,000, through β-globulin 90,000, and γ-globulin 156,000 to fibrinogen 400,000. In a discussion of the factors concerned in capillary permeability, Pappenheimer (1952) pointed out that the diameter of the pores in the capillaries is about 60 Å The smallest dimension of the plasma protein molecules is about 35 to 40 Å, which is regarded as the smallest size of particle which can be retained within the blood vessels Since none of the plasma protein molecules is spherical, none is concerned solely with the maintenance of plasma volume. The permeability of the capillary walls is subject to wide variation, albumin for example being largely confined within normal capillaries but leaving the unusually permeable capillaries of inflamed tissues as rapidly as water or sodium (Cope and Moore, 1944).

All the plasma substitutes in current use are colloids of large molecular weight; they are prepared by chemical synthesis or degradation and always contain a mixture of molecules of various sizes. The behaviour of a particular mixture depends on the relative numbers of molecules of different weights which it contains. The efficiency of a particular preparation of a suitable substance as a means of increasing the volume of fluid in circulation within vessels depends on whether it contains a sufficient proportion of molecules which are retained in the vessels for a worthwhile period of time.

Not much is known of the factors which govern the retention of colloid material within the vascular system. However, Grotte

et al. (1951) have shown that in the case of dextran there may be rapid diffusion of injected material from the plasma into the urine, interstitial fluid, lymph and intestinal secretions The rate and degree of loss are related to the molecular weight of the dextran molecules Bayliss *et al* (1933) studied the urinary excretion of protein by anaesthetised cats and rabbits and by the isolated perfused kidneys of dogs, they found that all the proteins excreted were of molecular weight less than 70,000 whereas all those retained had molecular weights in excess of 70,000 They further showed that the molecular weight, rather than the origin or nature of the molecule, was the critical factor in deciding whether the material crossed the glomerular membrane. Their conclusions regarding the critical size of molecule for renal excretion generally have been confirmed by Marshall and Deutsch (1950) and Metcalf *et al* (1954) have confirmed that the kidneys probably fractionate dextran at a molecular weight of about 70,000 Estimates of the molecular weight of preparations of dextran and P V P have been made on the basis of a relationship between intrinsic viscosity and molecular weight, but the interpretation of the relationship is subject to considerable variation. For this reason figures for molecular weights of plasma substitute fractions which are mentioned in this account are to be regarded as being arbitrary interpretations, though it is believed that they have some general validity [1]

All the available plasma substitutes, as prepared for therapeutic injection, contain mixtures of particles of varying molecular weight. Immediately after an injection most of the injected material will be found in the circulating blood. The smaller molecules, which are able to cross the capillary membrane, rapidly leave the circulating blood stream for the surrounding interstitial space, and an

[1] The Fikentscher K" value or viscosity coefficient is derived from the relative viscosity of a 1·0 per cent. solution of the material compared with distilled water at 20 C. according to the formula

$$\frac{\log U_{rel}}{C} = \frac{75K^2}{1+1\cdot5\,KC} = K,$$

where Urel = relative viscosity
C = concentration of substance in g per 100 ml.

Average molecular weight is then calculated from K.

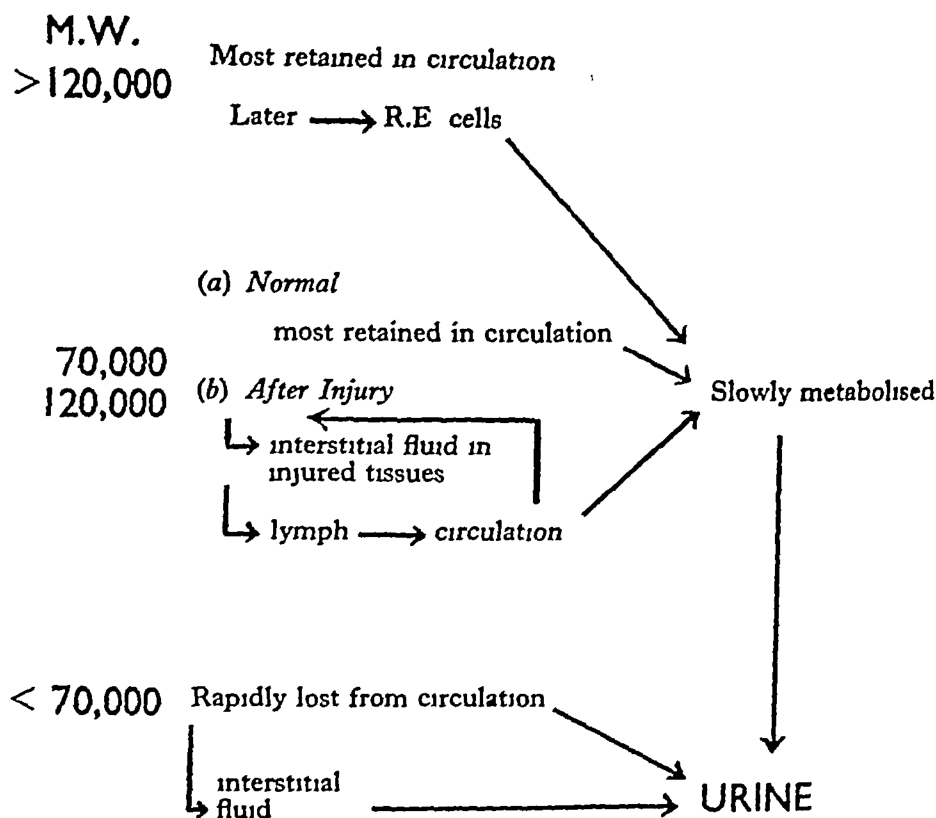
$$2\cdot303\,(0\cdot001K + 0\cdot000075K^2) = 0\cdot0016M^{0\cdot9}$$

when M = average molecular weight.

(From Ravin *et al.*, 1952).

unsteady equilibrium is established between plasma and interstitial fluid, about three-quarters of the smaller molecules being thus lost from the circulation. This process of equilibration throughout the extracellular fluid is disturbed, however, by the rapid coincident loss of small molecules from the renal glomeruli into the urine (Table XXII) As this urinary excretion lowers

TABLE XXII



the plasma concentration of small molecules, other molecules of similar size pass back into the plasma from the interstitial fluid to restore the disturbed equilibrium between plasma and interstitial fluid, and in due course are also excreted in the urine. It is clear, therefore, that the smaller molecules of a plasma substitute behave in a manner similar to inulin, which reaches an equilibrium between plasma and interstitial fluid within about an hour of injection, and about 95 per cent of which is excreted within 24 hours (Schachter *et al.*, 1950). The production of a lasting increase in plasma volume evidently depends on the injection of a sufficient dose of material with a molecular weight

too large to be excreted in the urine or rapidly lost into the inter stitial fluid The osmotic activity or water-holding capacity of a molecule in proportion to its weight diminishes as its size increases, but in the production of a plasma substitute it is essential that this activity is exerted within the vessels and some reduction in activity is permissible if the site of action can be controlled.

The permeability of the capillary membrane varies according to situation and circumstances Some of the material in a particular solution which exceeds the probable limit (M W 70,000) for rapid urinary excretion may be lost into interstitial fluid through even normal capillaries. Capillary permeability to protein is markedly increased after injury and in other kinds of inflammation, and in such circumstances it is likely that plasma substitutes of molecular weight up to about 120,000 midway between β- and γ-globulin, may readily be lost. It is believed that larger molecules than this are probably largely retained within the vessels until the material is metabolised, excreted after partial breakdown, or deposited in the reticulo-endothelial cells of the liver, spleen and lymph glands. It is undesirable to inject material the molecular weight of which exceeds 250 000 because of the adverse effects which are caused, in particular marked aggregation of red blood corpuscles and marked increase in blood viscosity and the erythrocyte sedimentation rate.

The ideal preparation for producing a lasting increase in circulating volume should contain minimal quantities of material of small molecular weight (less than 70 000) which will be readily and rapidly lost from the vessels into the interstitial fluid and the urine. The proportion of very large molecular weight material (above 250,000) also should be small to avoid undue increases in viscosity or aggregation and sedimentation of the red corpuscles. It seems reasonable to assume that the proportion of material of molecular weights between 70 000 and 120 000 which may be lost through the abnormally permeable capillaries of the injured tissues, should also be as small as possible. The bulk of the material should therefore be that with molecular weights between 120 000 and 250,000 which is retained to the greatest degree within the vessels This theoretical prediction has been confirmed by the work of Howard *et al* (1956) who injected very narrowly fractionated dextran of varying molecular weight. They found that when the molecular weight exceeded 129,000 only

4 per cent. or less of the dose appeared in the urine within 72 hours of the injection. Craig and Waterhouse (1955), using one of the same highly fractionated preparations, showed that the volume of distribution of their dextran in the body was similar to that of labelled red blood corpuscles or the venous haematocrit, but was less than that of the blue dye T. 1824 (which is adsorbed on to plasma albumin) or albumin labelled with radioactive iodine This also indicates that dextran of molecular weight exceeding 129,000 does not leave the capillaries as albumin does even in normal circumstances.

Crude preparations of the materials commonly employed contain molecules of weights ranging from a few thousands to several millions. To reduce the crude product to a preparation suitable for injection the material must be hydrolysed and the larger and smaller molecules must be removed by fractional precipitation. The manufacture of closely fractionated preparations of some substances is not easily practicable and is always relatively wasteful in material and costly in apparatus. The more closely the ideal is approached, however, the greater is the proportion of the injected material which remains in circulation and the smaller is the dose which must be injected to produce a satisfactory response. The comparison of experimental and clinical data has been made more difficult by incomplete descriptions of the composition of the preparations Differences in behaviour in regard to urinary excretion, blood concentration and haemodynamic effect may depend on the source of the material, degree of fractionation, the batch, dose and concentration as well as on the percentage molecular weight composition of the material in the solution. The results of animal experiments are difficult to interpret, because of species difference in tendency to reactions, and variations due to age and environmental conditions

The mode of action of plasma substitutes is not completely understood and may vary from one preparation to another. Haemodilution is a constant effect following the infusion of plasma substitutes and may be associated with reduction in the total plasma protein concentration. The change in protein concentration has been ascribed entirely to dilution (Bull, J. P., *et al.*, 1949) or to suppression of albumin synthesis (Rosenqvist and Thorsén, 1951), but there is evidence that the total quantity of protein in circulation may be increased in spite of the reduction in con-

centration (Hammarsten *et al*, 1953, Wilkinson and Storey, 1953) The state of protein nutrition of the body may be as important a factor in this type of response as it is in the alterations in total circulating protein after the infusion of saline (Shearburn 1942) The explanation of this mobilisation of plasma protein is uncertain, but it may be related to the expansion of the extracellular fluid which follows the infusion of saline and of small molecular plasma substitutes the consequent increase in the rate of turnover of extracellular fluid and of lymph formation may increase the rate of circulation of plasma protein Thus part of the effect of a plasma substitute on plasma volume might be due to this mobilisation of plasma protein.

In most of the reports of experiments in which the increase in plasma volume has been measured, the increase has varied widely with the same preparation in different normotensive animals or human subjects and has usually been less than the volume of dextran injected. The range of increment is as much as 200 to 1600 ml or more after the infusion of 1 litre of plasma substitute solution into adult subjects. This wide variation may be accounted for in several ways. Allergic reactions cause a large reduction in plasma volume (Wilkinson and Storey 1953 Koster *et al* 1957) and in normal volunteers there is probably a tendency towards the reduction of the increase in volume caused by the infusion. Techniques for measuring blood volume reflect in different ways what is happening in the circulatory system and may be misleading In addition there may be simply a wide individual variation in response which occurs with all types of preparation and is difficult to explain The molecules of dextran consist of long chains made up of a repeating pattern of smaller molecules linked together Their behaviour depends on their structure and may be modified by small changes in the repeating pattern. Structural differences such as the number and frequency of side chains and the type of linkage between molecules, may be related to differences in the strain of the polymerising organism (*Leuconostoc mesenteroides*)

Gum Acacia.—For many years before Bayliss (1916, 1919) suggested that it should be used for the treatment of shock in battle casualties, gum acacia in saline had been used for the maintenance of blood volume in laboratory animals. Gum acacia is a hydrophilic colloid derived from the natural gum of the acacia

thorn. It is believed to have the property of forming aggregates of its smaller molecules, which then are retained longer in the circulating blood. The selection of raw material and the preparation of solutions are largely empirical, but satisfactory preparations of a 6 per cent. solution in 0 9 per cent saline are available and give excellent clinical results. Although it is theoretically possible for the gum acacia molecule to be metabolised in the human body, there is no evidence that this occurs. It is known that it may be stored for long periods and in large quantities in the reticulo-endothelial cells of the liver and elsewhere, and a similar type of

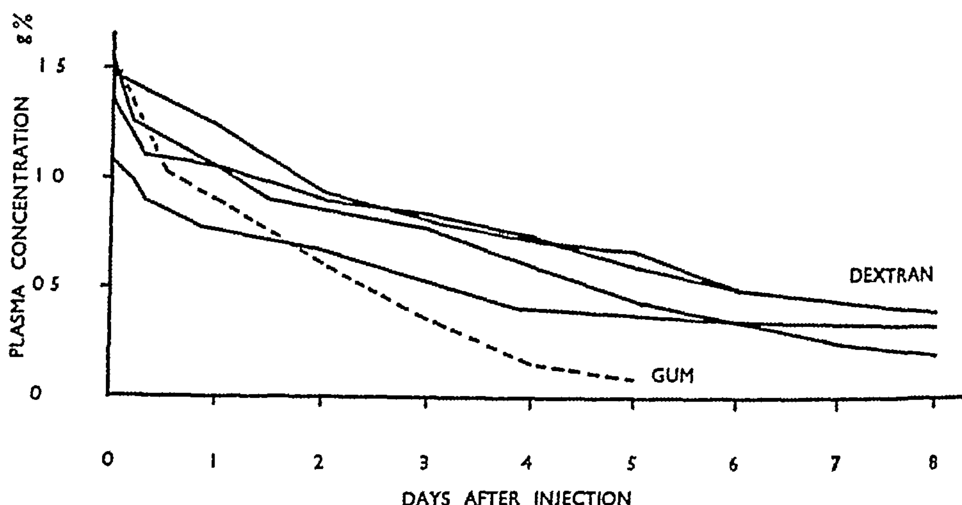


FIG. 11.—To show the rate of decline of plasma-dextran concentration after the injection of 1 litre of 6 per cent solution of dextran into four normal subjects The curve for gum acacia has been calculated from the data quoted by Amberson (1937).

storage has been observed after the infusion of other plasma substitutes Bollman (1951) found, however, that 10 years after the administration of very large quantities of gum acacia to dogs, their liver function was not impaired in spite of large hepatic deposits of acacia, and that these deposits had not produced a tissue reaction. Patients have been followed up for more than 20 years after infusions of gum acacia and are in good health.

Amberson (1937) reviewed a large number of reports on the use of gum saline and concluded that retention of gum acacia in the body and in circulation was good, 61, 43 and 25 per cent. of the injected dose being still in circulation 24, 48 and 72 hours respectively after injection (Fig. 11). Hartman (1951) recovered 25 per

cent. of the injected material from the urine in the first 24 hours after injection and 60 per cent. in 7 days Anaphylactic and urticarial reactions to gum acacia have been recorded at intervals since its introduction and have done much to discourage its use. Provided that reliable preparations are employed, it is a valuable and safe agent. The chief disadvantages arise out of the lack of knowledge of the chemistry of gum acacia, the empirical methods of production and the potentially uncertain supply of raw material.

Gelatin.—Gelatin, derived from the bones and skins of cattle and pigs, was formerly used for the treatment of shock. Because of the small size of the gelatin molecule, and the consequent rapid excretion of most of the injected material in the urine its effect on blood volume was so transitory that the use of gelatin has now been abandoned.

Polyvinylpyrrolidone (P V.P)—This is a synthetic water soluble substance made from formaldehyde, acetylene and ammonia. It is also known as Periston Kollidon or Polyvidone. It was developed in Germany and first used there as a plasma substitute by Hecht and Weese (1943) It was usually employed as a 3 5 per cent. solution in a mixture of minerals in the same concentrations as those in which they are found in the blood the viscosity and osmotic pressure exerted by such a solution resemble those of plasma. P V P is not metabolised in man. Such a high proportion of the injected material was excreted in the urine that its effect on blood volume was of short duration Fractionation to increase the proportion of material of large molecular weight would increase the amount retained in the body and deposited in the reticulo-endothelial cells The use of P V.P is declining

Dextran.—Dextran is a polysaccharide composed of glucose molecules joined in a long branched chain by two types of glucosidic linkage. It is a natural product of the action of the bacterium *Leuconostoc mesenteroides* on decaying vegetable matter In nature, dextran occurs as masses of ropy slime and has for many years been a nuisance in the sugar beet industry Native dextran varies in molecular weight from a few thousands to millions, and is toxic. The pattern of the branching of the molecular chains is related to the strain of polymerising organism and to the substrate. In 1937 Stacey suggested that, by reason of

its molecular structure, dextran might be useful in a similar manner to gum acacia as a means of restoring plasma volume. In 1941 Gronwall and Ingelman independently also suggested that dextran would be of value as a plasma substitute and undertook the necessary hydrolysis and fractionation to reduce molecular size to within safe limits (Gronwall and Ingelman, 1944, 1945) Subsequently dextran was subjected to extensive clinical trials in Sweden (Bohmansson *et al.*, 1946; Thorsén, 1949) and elsewhere, and has been widely adopted as a routine plasma substitute.

Dextran is usually employed as a 6 per cent. solution in 0·9 per cent saline. It has been repeatedly shown that retention of dextran in the blood stream is directly related and excretion in the urine is inversely related to molecular weight. Unfortunately agreement has not yet been officially reached on the optimum composition of dextran solutions for clinical use. This is possibly because an anxiety to avoid urticarial reactions has led to the employment of solutions containing comparatively small percentages of the material of molecular weight between 125,000 and 250,000, which is almost entirely retained within the vessels. In early preparations the proportion of smaller molecules was comparatively high and up to 50 per cent. or even more of the injected dextran was excreted in the urine within 24 hours Later, closer fractionation of the hydrolysed dextran resulted in at least one commercial preparation of which only 10 per cent. was excreted within 24 hours and 15 to 20 per cent. in 48 hours (see Fig. 11). Up to 70 per cent remained in circulation after 24 hours and 30 per cent after five days (Wilkinson and Storey, 1953) The current Swedish and American preparations have in general a lower average molecular weight than those made in Britain and leave the blood stream and are excreted in the urine more rapidly. Although minute quantities of dextran are detectable in the body by serological methods for several months after an injection, it finally disappears from the body and only temporary histological changes attributable to it have been described. Pulaski (1952) injected dextran labelled with ^{14}C and showed that dextran is metabolised in man as well as in animals. Terry *et al.* (1953) recovered over 90 per cent of the injected ^{14}C, 25 per cent. as carbon dioxide and 40 per cent. in the urine. They and Gray (1953) found the highest concentrations of dextran in the liver, lymph glands, adrenals and spleen and that the dextran dis-

appeared most rapidly from the liver The elimination of ^{14}C as carbon dioxide continued after all dextran had disappeared from the blood.

Reactions following the use of dextran in the treatment of shocked patients are very rare, a rate of only 0 8 per cent. after 14,000 infusions being recorded in Sweden by Thorsén (1949) during a period when the incidence was 8 2 per cent. for whole blood transfusion. Maycock (1952) reported a reaction rate of 1 88 per cent. in 1647 British patients to whom dextran was administered However, in normal subjects with normal blood volumes reactions are very common after infusions of dextran Gropper *et al.* (1952) found a reaction rate of 40 per cent with Swedish dextran in normal subjects, and Wilkinson and Storey (1953) reported a rate of 100 per cent. These reactions can be resolved into two components or phases (Heisto and Lund, 1953, Wilkinson, 1955), one characterised by urticaria coming on during the infusion or soon after it is completed and lasting for up to two hours, and the other by vasomotor disturbances which appear after the infusion is completed. The vasomotor disturbance closely resembles that described by Martin (1954) following the infusion of human albumin There is a sensation of fulness of the head made worse by standing up, headache, discomfort in the chest on exertion and venous engorgement.

Even in the absence of any sign of a reaction the administration of solutions of highly fractionated dextran to subjects with normal blood volumes gives rise to circulatory overloading with headache, precordial pain and tachycardia on exertion, these effects may persist for several days following the injection and afford further evidence of the prolonged retention of such highly fractionated preparations in the blood stream. Haemodilution is a constant sequel to the infusion of dextran solution except in normal subjects who react. During the reaction, after an initial haemodilution there is marked haemo-concentration with reduction of plasma volume and the quantity of plasma protein in circulation This effect gradually passes off and between 12 and 24 hours after the onset of the reaction there is a return to the original degree of haemodilution as plasma volume increases and the quantity of protein in circulation is restored. These effects are now thought to be due solely to the rapid loss of plasma from the circulation following a sudden change in capillary

permeability, induced by the antigenic reaction to the injected dextran

Although the serological activity of dextran is clearly established (Hehre and Sugg, 1950; Neill and Abrahams, 1951; Kabat and Berg, 1952), there is also evidence that this activity varies with different types of dextran. Amspacher and Artz (1951) for example found that a dextran synthesised by the B512 strain of organism did not cause reactions even when injected into normal volunteers, and this has been confirmed (Wilkinson, 1956 c) even with large molecular weight dextran of this type. It seems likely that the strain of polymerising organism, and thus the structure of the dextran molecule, is of greater importance than the molecular weight of the dextran; if this is correct it would dispose of the main objection to the use of large molecular weight dextran, an alleged much higher incidence of reactions of all kinds.

Prolongation of the bleeding time has been reported after the infusion of large volumes of dextran solutions, and on a few occasions, even after the infusion of less than a litre This complication is more common after the infusion of more dextran than is necessary to restore blood volume to normal and seems to be due mainly to the overloading of the circulation. Although some interference with blood coagulation is associated with the presence of critical concentrations of any macromolecule, no other specific effect of dextran on blood clotting has been described.

Effect of Plasma Substitutes on Blood Grouping.—All large molecular colloids to some extent cause aggregation of the red blood corpuscles and false rouleaux formation, and may thus interfere with blood grouping and compatibility tests. A sample of blood should therefore always be withdrawn before a plasma substitute is injected; if this is not done, blood grouping can still be carried out, but extra care is required in the interpretation of the results

Mode of Use.—To produce the optimum effect on blood volume, a plasma substitute should be injected rapidly. At first only as much should be given as is necessary to raise the blood pressure to within normal limits, and then sufficient should be given to prevent further reduction of blood pressure Maintenance doses also should be given fast. It is a mistake to give them slowly, especially if the preparation is not closely fractionated,

because the small molecules may then escape from the blood stream almost as fast as they are injected, while there may be a gradual and undesirable accumulation of the largest molecules, the resulting increase in blood volume is not as great as it would be after a more rapid injection of the same volume of solution The intravenous infusion should be kept running slowly with glucose solution until there is no longer any need for supplementary replacements

Since the administration of large volumes of plasma substitutes causes haemodilution, it may give rise to marked anaemia, especially when there has been considerable bleeding In addition to a plasma substitute, the administration of whole blood may thus often be desirable and, after the loss of very large quantities of blood, may be imperative. It is probably wise to administer whole blood whenever the haemoglobin concentration falls below 60 per cent. of normal

Undoubtedly the widest use of plasma substitutes will be made in the treatment of burns. Rosenqvist and Thorsén (1951) showed that even the earlier Swedish preparation of dextran, containing a high proportion of low molecular weight dextran, was an adequate replacement for the plasma lost after burning especially when blood also was administered. Recent experiences with a more highly fractionated preparation, with a higher percentage retention in the blood stream, have shown that dextran alone is a satisfactory substitute for plasma in the treatment of burn shock (Wilkinson, 1958) Restoration of the blood pressure to within normal limits and its maintenance can be achieved with smaller volumes of dextran than of plasma. In view of the comparatively poor response which often follows plasma infusion in burn shock (Rhoads *et al.* 1941) dextran is preferable to plasma for this purpose. Consistently good results in the resuscitation of shocked burned patients have been obtained in the past with reliable preparations of gum saline, which also is superior to plasma.

Plasma substitutes are of value to supplement blood transfusion and so to reduce the requirements for whole blood. They can be employed instead of blood when the volume required does not exceed 1 litre, and are very useful for starting the resuscitation of severely shocked patients in the interval while blood compatibility tests are being carried out.

THE MAINTENANCE OF NUTRITION

Parenteral Feeding.—It was probably Sir Christopher Wren who in 1657 first suggested that animals and man might be kept alive by the intravenous injection of nutriment of various kinds and soon afterwards his friend Dr. Robert Boyle injected warmed sack into the veins of a dog (Boyle, 1663). In spite of the success of the original experiment, intravenous feeding, like blood transfusion which Wren also encouraged, languished for more than 200 years before the widespread clinical adoption of the continuous-drip intravenous infusion prepared the way for the introduction of protein hydrolysates and fat emulsions. Strictly speaking the term "parenteral feeding" implies the provision of the complete daily requirements of energy, protein, electrolytes and vitamins by intravenous infusion. Clinical practice falls short of this objective. Even the provision of energy alone in the form of carbohydrate or fat is subject to great variation and is usually far from adequate.

In an ideal mixed diet there should be sufficient protein to provide 12 5 per cent. of the total calories (70 g. in a 2240-calorie intake). It is well established that the full utilisation of dietary protein depends on the simultaneous provision of an adequate supply of non-protein calories, in the absence of which some, or even all, of the protein is used for energy purposes and so is wasted as a source of protein components This principle applies equally to the use of protein or protein components in intravenous feeding; unless the protein is accompanied by a source of calories it will be deaminated, the nitrogen will be converted to urea and the residues used as a source of calories.

A healthy adult at rest in bed probably requires about 2100 calories per day, but after injury the basal requirement is greater (Cuthbertson, 1945). The chief limiting factor in the parenteral supply of a complete daily quota of calories is the volume of fluid which can be tolerated when administered by intravenous infusion. In the normal uninjured adult the diuretic response to the infusion of 5 or 6 per cent. *glucose* solution is rapid and complete, but after injury the ability to excrete water is limited, and not more than about 2 5 litres of glucose solution per day can be safely administered without some water being retained. When 5 per cent. glucose solution is employed, only 125 g. of glucose providing 448

calories can be supplied by the infusion of 2 5 litres of solution but this is sufficient to reduce protein catabolism due to starvation to the minimum. When 10 per cent. glucose solution is employed, the total glucose available for energy purposes may be reduced by the loss of up to 30 per cent. of the glucose in the urine For solutions of similar strength, glycosuria is less marked with *invert sugar* than with glucose (Lawton *et al*, 1951), and is even smaller when *fructose* is employed (Weinstein and Roe, 1952) because of the more rapid removal of fructose from the blood The urinary loss of carbohydrate is reduced by a slow rate of infusion, because the blood glucose concentration is lower, but the incidence of thrombophlebitis is increased as the duration of a glucose infusion is prolonged The slow infusion of concentrated glucose solution (50 per cent.) into the great veins offers one means of providing 1500 calories per day in a volume of only 1 litre, but this method of administration is not free of risk and so is unsuitable for routine post-operative use and should be reserved for the critical circumstances of the anuric patient.

The intravenous infusion of *ethyl alcohol* has also been employed as a means of providing calories (Mueller, 1939, Rice *et al*, 1952) Alcohol can replace fat and carbohydrate in the diet (Atwater and Benedict 1902), and its rate of oxidation was shown by Mellanby (1919) to be independent of the other foodstuffs being metabolised, he found that 8 0 g (10 ml.) of ethyl alcohol can be oxidised every hour, providing 7 0 calories per gram of alcohol oxidised Following the oral consumption of alcohol there is a rapid initial rise in blood alcohol concentration which then slowly declines in a linear fashion (Mellanby, 1919) When alcohol is administered at a steady rate by intravenous infusion, the blood alcohol concentration rises slowly to a degree dependent on the rate of infusion (Eggleton, 1940) provided this rate does not exceed the usual rate of oxidation of 8·0 g (10 ml) per hour, there are no adverse effects such as inebriation (Moore and Karp, 1945, Wilkinson 1955) Up to 192 0 g (240 ml.) of ethyl alcohol can be administered in 24 hours which will provide over 1300 calories, and 3 litres of a solution containing 6 per cent. of alcohol (180 ml.) have been repeatedly administered over 24 hour periods to severely ill and wasted patients without adverse effects (Table XXIII) The metabolism of alcohol is said to be promoted by the administration of fructose (Martensen Larsen, 1954), this

property together with its rapid removal from the blood stream makes fructose the best sugar to combine with alcohol and amino acids for parenteral administration.

Before being administered by intravenous infusion, whole protein other than plasma must be hydrolysed to amino acids and small peptides. *Protein hydrolysates* for this purpose may be prepared by the acid or enzymatic hydrolysis of milk or meat protein, care being taken to ensure that any deficiencies of "essential" amino acids in the resulting mixture are made up by

TABLE XXIII

Quantities of Fat, Carbohydrate and Alcohol necessary to supply 2100 Calories per 24 hours

	Calories/g	*Solution per cent.*	*Litres per 24 hours*
262 5 g fat	8 0	15	1 75
560 g glucose or fructose	3 75	5 10 40	11 2 5·6 1 4
300 g. ethyl alcohol (375 ml)	7 0	6	6·25

the addition of supplements. Solutions containing synthetic amino acids in theoretically desirable and nutritionally adequate proportions and concentrations have also been used, alone or combined with vitamins and various minerals. It has been the custom to employ a solution containing 5 or 10 per cent. of amino acids combined with glucose as the source of supplementary or protective calories. Opinion is divided regarding the rate at which such solutions should be infused; rapid infusion of the whole daily intake during a few hours is said to cause less discomfort to the patient, but is accompanied by a larger urinary wastage of both nitrogenous material and glucose. Steady but slower infusion throughout the 24 hours leads to less urinary wastage but increases discomfort and thrombophlebitis. The urinary nitrogen excretion rises even in patients who have been severely depleted of protein. In normal subjects the basal daily requirement per 1 73 square metre body surface is of the

order of 10 g nitrogen and 1600 calories, average basal figures for clinical use are 70 to 80 g protein (11 2 to 12 8 g nitrogen) and 1800 to 1900 calories.

Provided it has been stored at room temperature for 6 months the administration of human *plasma* no longer carries the risk of causing infective hepatitis (Allen 1955) There is therefore less objection to using human plasma as a source of protein in malnourished patients. Stemmer *et al.* (1955) have shown that when injected intravenously plasma protein is as adequate for maintaining the growth of puppies as is the consumption of an equal quantity of horse meat In their experiments as in human nutrition, the most important limiting factor seems to have been the quantity of plasma which it was reasonable to inject each day in addition to a parenteral source of adequate non-protein calories They also confirmed the earlier observation of Allen *et al* (1948) that anaemia appears within a week of beginning the daily infusions of plasma, which may have to be interrupted while packed cells are transfused to correct the anaemia. It cannot be too strongly emphasised however, that the intravenous use of human plasma as a source of protein is completely unjustified, and almost certainly valueless unless at the same time an adequate quantity of non-protein calories is also injected or consumed, for the typical 70 kg adult male an adequate quantity is at least 1800 calories per day or 75 calories per hour

A fat emulsion is the most compact source of calories for intravenous administration can be used repeatedly and does not regularly cause thrombophlebitis as do strong sugar solutions Fat emulsions do not exert any osmotic effect and so can be employed at high concentrations without withdrawing water from the tissues as strong glucose solutions do Since 1946 various types of fat emulsion have been used by Stare and his colleagues and by others (Van Itallie *et al* 1952, Kaute, 1958) but the main disadvantages were frequent reactions and instability of the emulsion which had only a short 'shelf life' Recently a reliable and safe commercial preparation (Lipomul) has become available. In this, 15 per cent. cottonseed oil is combined with 4 per cent. glucose to provide 1350 calories per litre of emulsion. There is evidence that fat administered by intravenous infusion can be rapidly metabolised in various animals and man When trilaurin (Geyer *et al.*, 1948) or esterified palmitic acid (Lerner *et al.* 1949)

is labelled with ^{14}C and administered intravenously in an emulsion $^{14}CO_2$ appears rapidly in the expired air. Shafiroff *et al.* (1951) found deuterium in the water vapour of expired air and in the urine after tristearin containing deuterium had been injected into the veins of human subjects. Johnson *et al* (1952) found that 75 per cent of the fat emulsion they injected into normal volunteers over a period of 2 hours was removed from the circulating blood before the infusion was finished and the rest within another 8 hours The fat disappears more rapidly when the metabolic rate is high, for example in thyrotoxicosis, and more slowly in patients with impaired renal function. Few metabolic balance studies involving the intravenous infusion of fat emulsions into human subjects have been reported, but Upjohn *et al.* (1957) found that when a modern emulsion is added to an otherwise adequate intake of calories there is an increase in nitrogen retention. In malnourished patients the degree of the nitrogen retention seems to depend on the basal protein intake and the degree of nutritional depletion. Stare and his colleagues (Van Itallie *et al*, 1952) kept a severely injured man alive for 67 days by infusions of fat emulsion, glucose and protein hydrolysates. Abbott *et al.* (1957) gave fat emulsions combined with amino-acids, glucose and alcohol to well-nourished patients who had been submitted to partial gastrectomy, and were able in this way to abolish starvation during the first post-operative week; they also found that they could discharge their patients home several days sooner than otherwise would have been possible. It is of interest that although Abbott *et al.* were able to reduce very greatly the loss of nitrogen in the urine during the first week after gastrectomy they could not consistently maintain positive nitrogen balance or nitrogen equilibrium in their patients.

The same care to avoid bacterial contamination is needed with fat emulsion as with amino-acid solution or blood The fat emulsion should never be mixed with other solutions before or during administration, the simplest arrangement being to use a 3-way tap on the delivery tubing. Fat emulsion has been injected repeatedly into adults and into infants soon after birth with very few serious reactions Pyrexia is the most frequent complication, the temperature beginning to rise during or just after the infusion, reaching a peak within an hour or two and returning to normal within 8 hours. Sometimes the rise in temperature is accompanied

by headache or nausea and more rarely vomiting, loss of appetite or even diarrhoea. Pain in the back and urticaria are very rare, but anaemia is common when repeated daily infusions are given These reactions usually subside rapidly when the infusion is stopped after a short interval there is seldom any objection to restarting the infusion at a rather slower rate. Levenson *et al* (1957) observed severe reactions in two normal volunteers after 14 and 21 days of daily infusions of 1200 ml of fat emulsion. In each there were signs of gastro-intestinal bleeding and in one of some alteration in blood coagulation processes, accompanied by a general feeling of illness and tiredness with pyrexia. In both the reactions subsided slowly when the infusions were stopped Hawk (1957) has reported an incidence of less than 5 per cent. of reactions after 2300 infusions of this fat emulsion

Solutions which have been employed in parenteral feeding are shown in Table XXIV In solution A, the type of preparation which has been most widely used in the past, the combination of 5 per cent. glucose with 5 per cent. amino acids provides only 387 5 calories per litre of which more than half are derived from protein. When 10 per cent. glucose is used up to 30 per cent. of the carbohydrate may be lost in the urine if the solution is administered rapidly but even without this loss a litre of the solution contains only 536 calories The substitution of 6 per cent. ethyl alcohol for glucose (B) increases the non protein calories to over 60 per cent. of the total but 4 litres of this solution would be required to supply 2100 calories involving the oxidation of 240 ml. (192 g) ethyl alcohol which is close to the upper limit of tolerance. The combination of glucose and alcohol (C) increases the non-protein calories to more than 70 per cent. of the total, and requires the oxidation of only 180 ml (144 g) of ethyl alcohol per 24 hours when 2100 calories are provided. Wastage of carbohydrate in the urine is less with fructose than with invert sugar or glucose The combination of 6 per cent. ethyl alcohol with 10 per cent. fructose will provide 911 calories per litre, of which only 25 per cent are derived from protein 2 5 litres of this solution contain 150 ml. of ethyl alcohol per day which the adult body can readily oxidise without adverse effects (Wilkinson, 1955)

It is usual to administer up to 2500 ml of solution containing 5 per cent. amino acids and glucose or other sugar in each 24-hour period, 500 ml should be administered every 4 or 5 hours and

for a short time between each bottle of solution containing glucose up to 100 ml. of a fluid which does not contain glucose, such as isotonic (0·9 per cent.) saline, may be infused. This short interval

TABLE XXIV

Solutions used for Intravenous Feeding

		g per litre	*Calories per litre*	*% Total calories*
A	5% glucose	50	187·5	48·4
	5% amino acids	50	200·0	51·6
	per litre		387·5	
B	6% alcohol	48	336·0	62·7
	5% amino acids .	50	200·0	37·3
	per litre .		536·0	
C	5% glucose	50	187·5	24·6
	6% alcohol	48	336·0	47·8
	5% amino acids .	50	200·0	27·6
	per litre		723·5	
D	10% fructose .	100	375·0	41·0
	6% alcohol .	48	336·0	36·8
	5% amino acids .	50	200·0	22·2
	per litre .		911·0	
E.	15% cottonseed oil	150	1200·0	88·8
	4% glucose	40	150·0	11·1
	per litre		1350·0	

greatly delays the onset of the chemical thrombophlebitis, which follows the prolonged infusion of glucose solution. This rate of infusion is suitable also for solutions which contain 6 per cent. ethyl alcohol, the blood concentration of which is then unlikely to rise much above 40 mg per 100 ml; 500 ml. of a 6 per cent. solution of alcohol contains 30 ml. which could be completely oxidised in 3 hours.

The best parenteral means of supplying energy now available is by the intravenous administration of a stable fat emulsion, such as Lipomul which contains 15 per cent. cottonseed oil and 4 per cent. glucose. A litre of this emulsion provides 1350

calories (E, Table XXIV), and when combined with a litre of solution containing 5 per cent. amino acids and 5 per cent glucose (A, Table XXIV) the total mixture supplies 50 g amino acids and a total of over 1700 calories, of which only 11 5 per cent. come from the amino acids and almost 70 per cent. from the fat. The fat emulsion should precede the amino-acid solution and in an adult 500 ml. of emulsion should be infused over a period of 4 or 5 hours and be followed by 500 ml of the amino-acid solution at a similar rate.

Solutions of amino acids and carbohydrate contain practically no sodium or potassium, and are not of any value in correcting losses of body fluids by vomiting or from a fistula Usually the daily output of urine is about equal in volume to the quantity of hydrolysate solution which is administered. During the infusion of a protein hydrolysate the skin becomes flushed and warm and patients are often drowsy, there may be headache, loss of appetite is common and is associated with a meaty taste in the mouth. Most hydrolysate preparations are brown in colour, possibly because of so-called "caramelisation" of the glucose during autoclaving, the urine also is brown in colour and may have a characteristic meaty odour

Protein hydrolysates usually contain little if any potassium, sulphate, phosphate or other components of protoplasm except amino-acids and peptides and it is unlikely that tissue synthesis can occur without a supply of these important constituents It is unusual also for vitamin supplements to be administered along with protein hydrolysates Apart from the inadequate provision of calories, the most important factor which hinders the conversion of intravenously administered amino acids into new protein tissue is, however the absence of a stimulus to tissue formation, or perhaps more important still the presence of a stimulus to catabolism of tissue. The way in which healing occurs in damaged tissues while apparently normal tissue is destroyed is not understood. There seems to be little reason to justify the hope that exogenous protein administered intravenously will be converted to new tissue in a body which is destroying its own uninjured muscles. Apart from the mitigation of the effects of starvation and its influence in making fat metabolism more complete it is still uncertain whether the administration even of glucose is of any real value during the catabolic phase after injury The

organism must obtain energy for essential metabolism if it is to survive, and in the absence of glucose administration it obtains sufficient energy from its own tissues. While there is evidence that the administration of large enough amounts of glucose or fructose combined with fat will avoid most of the protein catabolism due to starvation, and probably reduce the oxidation of storage fat, there is no other justification for the routine administration of glucose solution as a nutritional measure after injury or surgical operations, or for the belief that "a little is better than none at all".

There are two important factors on which the utilisation of administered protein depends, regardless of the type of protein or the route of administration, both of which may also be of significance:

(1) The hormonal state of the body must be favourable, only in the anabolic phase is the emphasis on tissue formation.

(2) The protein must be accompanied by sufficient calories to prevent its wastage by conversion to energy.

So long as the value of intravenous feeding is uncertain, the indications for its use are limited to the few states in which a patient is unable to eat or digest food, for example in the treatment of ulcerative colitis, fistulas of the small intestine, or severe malnutrition, or in severe acute liver disease, when nausea prevents the consumption of food or fluid.

Jejunostomy.—There is a good deal of prejudice against the use of jejunostomy feeding, and it is seldom employed. In oesophageal obstruction its use avoids the necessity for interference with the obstructing lesion either by dilatation or intubation, and allows of the maintenance of a high intake of protein and calories. It is said to interfere with the free choice of a loop of jejunum for anastomosis to the oesophagus after resection of the obstructed segment. This difficulty can be avoided by making the jejunostomy in a loop lower than usual A jejunostomy does not have some of the disadvantages of a gastrostomy: subjective sensations are fewer during and after feeds and regurgitation does not occur Feeding does not have to be interrupted during the immediate post-operative period. In patients with gastric, duodenal, biliary or pancreatic fistulas, in addition to enabling food intake to be continued, it has the immense advantage that collected discharges from the fistula can be replaced in the intestine through

the jejunostomy and disturbances of body fluid equilibrium are largely avoided Cramping pain may be severe during the first few days, but can usually be prevented by avoiding strongly hypertonic fluid feeds (Allen and Welch, 1941) Diarrhoea is often troublesome no matter what type of feed is employed, but can be controlled by the administration of opium (Tinct. opii 10 to 15 minims, 4 to 6 times per day) and kaolin (1 oz. every 4 hours after a feed as an emulsion, washed into the tube with water) Some of the feeds which have been proposed are unnecessarily complicated (Hollander s mixture 12 ingredients, Ivy s mixture, 13 ingredients) A simple mixture of whole milk, lactose and dried skimmed milk powder with a vitamin supplement serves well and is nutritionally adequate, a patient with a benign oesophageal stricture has been maintained in positive nitrogen balance and at a steady weight for 6 weeks with this mixture (Wilkinson, unpublished data)

The jejunum is intolerant of fat, and the fat content of feeds should be kept low The caloric value of whole milk is too low for adequate nutrition to be maintained on this alone. Since there is no impairment of the digestive capacity of the intestine, there is no reason to use protein hydrolysates in jejunal feeding

A mixture containing 2 pints of fresh whole milk, 240 g lactose and 200 g dried skimmed milk powder will provide a daily intake of 2400 calories, 120 g protein, 1 76 g (76 mEq) sodium, 4 48 g (116 mEq) potassium and 3 38 g (90 mEq) chloride. This mixture should be made in the cold by the addition of the lactose and dried skimmed milk to the whole milk the dried milk goes more readily into solution if mixed with gradually increasing quantities of whole milk. After the mixture has been stirred, the supernatant solution is poured off and sufficient cold water is added to dissolve the sediment the two solutions are mixed together and kept in a refrigerator until used To prevent intestinal spasm and the deposition of sediment in the tubing the feeds should be warmed before administration.

A Witzel type of jejunostomy serves well and may be made under local anaesthesia. The first feed of 120 ml of 5 per cent glucose solution should be injected as soon as the operation has been completed, and thereafter two-hourly feeds are given. At first 60 ml. of milk mixture, followed by 60 ml of 5 per cent. glucose solution or water are run in from a funnel under gravity

After 12 or 24 hours it is usually possible to increase the quantities to 90 ml and then to 120 ml. of milk mixture, followed on each occasion by an equal volume of water or glucose solution. The total water intake amounts to 2800 ml. in 24 hours, and when glucose solution is used to wash the tube after a feed an additional 260 calories are provided Such a large water intake is desirable in all patients whose intake of protein is high, regardless of the manner in which they receive the protein; when the water intake is too low for the complete excretion of the end-products of metabolism there may be a deterioration in the clinical condition of the patient with elevation of the extracellular concentration of urea, sodium and chloride; improvement follows an increased water consumption and the reduction of the protein intake. If jejunal feeding is continued for more than a week, a complete vitamin supplement should be administered, preferably as a compound mixture in syrup, which is diluted with water to avoid jejunal irritation. When there is potassium deficiency, up to 12 g. potassium chloride (156 mEq. potassium) may be added per day to the water used to wash the tube after feeds The addition of sodium chloride to the feeds usually causes severe diarrhoea. Fluid collected from fistulas or by gastric aspiration can be run into the jejunostomy in the intervals between feeds, when this is done, to reduce the risk of blockage the tube should be washed clean with water before the milk mixture is run in.

THE PROVISION OF WATER

The normal minimum daily water requirement is 1500 ml When oral intake has been stopped, this may be supplied by the intravenous infusion of a 5 per cent. solution of glucose, up to 2 litres being administered in each period of 24 hours Such a solution is usually acid in reaction, but apart from its irritant effect on the vein used, this acidity does not seem to matter. The administration of glucose solution requires careful control: the volume should not exceed the estimated requirements of water for insensible loss by vaporisation and for urine formation, glucose solution is not of any use to replace lost gastro-intestinal secretions. The value of glucose solution as a replacement for loss of body fluids by sweating is limited by the losses of sodium and chloride in the sweat. The daily administration of 2 litres of glucose

solution for several days after major operations does not reduce the eventual loss of weight and body constituents, and does not relieve thirst. Glucose solution should not be administered intravenously to patients with anuria, except when during the diuretic phase, persistent vomiting prevents the replacement by drinking of water lost in the urine. It is liable to produce water intoxication when there is oliguria after surgical operations or in the presence of severe infection of any kind, especially in elderly patients or when renal function is impaired by chronic renal disease. After the subcutaneous administration of solutions of glucose or other sugars even with the addition of hyaluronidase, absorption is delayed while equilibrium is reached between the depot of solution and the extracellular fluid, when extracellular fluid volume is reduced or the volume of solution infused is large, undesirable shifts of extracellular fluid may be induced by this equilibration.

THE REPLACEMENT AND MAINTENANCE OF ELECTROLYTE CONTENT

Before the administration of solutions of electrolytes (Table XXV) is begun, an attempt should be made to estimate the total loss of cations and water and the type of accompanying anion disturbance, as well as the probable normal and abnormal daily requirements of the individual patient.

Sodium.—ISOTONIC (0·9 PER CENT.) SALINE contains 153 mEq per litre each of sodium and of chloride and is therefore not strictly isotonic with the concentrations of sodium (about 140 mEq. per litre) or chloride (about 103 mEq. per litre) in extracellular fluid. This solution, however, is nearly isotonic with the total cation and anion of extracellular fluid (about 155 mEq. per litre). When isotonic (0·9 per cent.) saline is used to replace a loss of extracellular fluid, its most important effect is to inceases the quantity of sodium and water although it provides an excess of chloride and thus tends to produce acidosis, this tendency is usually compensated by an increased renal excretion of chloride. "Isotonic" saline (0·9 per cent.) is not a "normal" solution in the chemical sense, for such a solution would contain one gram molecular weight of sodium and chloride per litre (58.5 g. per litre.) Isotonic saline is used for the replacement of acute losses

Table XXV

Composition of Solutions used for Electrolyte Replacement

	Constituents	*g/100 ml*	*Concentration of Components* *mEq/litre*				
			Na	K	Cl	HCO_3	Lactate
Extracellular fluid			140	5·0	103	25	—
Isotonic (0·9 per cent) saline	NaCl	0·9	153	—	153	—	—
Hypotonic (0·45 per cent) saline	NaCl	0·45	76·5	—	76·5	—	—
1/5 normal (0·18 per cent) saline	NaCl	0·18	30·25	—	30·25	—	—
Hypertonic (5·85 per cent) saline	NaCl	5·85	1000	—	1000	—	—
Sodium lactate (1/6 molar)	Na lactate	1·86	167	—	—	—	167
Potassium chloride	KCL	0·55	—	74	74	—	—
Saline lactate (Hartmann or Darrow)	NaCl Na lactate	0·6 0·62	102 56	— —	102 —	— —	— 56
			158	—	102	—	56
Ringer lactate	NaCl Na lactate KCL $CaCl_2$	0·6 0·31 0·03 0·02	102 28 — —	— — 4 —	102 — 4 4	— — — —	— 28 — —
			130	4	110	—	28
Darrow's solution (K lactate)	NaCl Na lactate KCL	0·4 0·62 0·27	68 56 —	— — 36	68 — 36	— — —	— 56 —
			124	36	104	—	56
Sodium and potassium chlorides	NaCl KCL	0·6 0·27	102 —	— 36	102 36	— —	— —
			102	36	138	—	—
Potassium phosphate and saline	K_2HPO_4 KH_2PO_4 NaCl	0·45 0·1 0·55	— — 94	52 7 —	— — 94	— — —	— — —
			94	59	94	—	—

of extracellular fluid by vomiting or by diarrhoea The administered fluid is rapidly distributed throughout the extracellular fluid. Although some increase in plasma volume accompanies the rapid infusion of saline this increment is short lived, since about three-quarters of the administered saline is eventually distributed in the interstitial fluid and only one-quarter in the intravascular fraction of the extracellular fluid.

GLUCOSE SALINE.—The combination of 5 per cent. glucose and 0·9 per cent. sodium chloride as glucose saline results in a hypertonic solution, since both constituents are present in an isotonic concentration

HYPOTONIC SALINE.—Solutions of sodium chloride weaker than 0·9 per cent. may be used when the need for water exceeds that of sodium and it is desired to prescribe only one solution for use throughout the 24 hours This method has the advantage of steady administration of a particular mixture and avoids the sudden loading of the body with a large quantity of sodium chloride during a brief period followed by a long infusion of glucose solution So-called half normal saline" (0 45 per cent.) is prepared by mixing equal volumes of 0 9 per cent. saline and 5 per cent. glucose solution ' Fifth normal saline" containing 0·18 per cent. sodium chloride is widely used in continuous infusions in paediatric practice. In effect, the same end is achieved by those who employ for routine post-operative infusions in adults the daily ration of 4 pints of 5 per cent. glucose solution and 1 pint of 0·9 per cent. saline The use of hypotonic saline is liable to induce a false sense of security on the part of the clinician.

HYPERTONIC SALINE.—This is of value in water intoxication, or when an excessive volume of water has been administered to a patient with sodium depletion. Usually a 5 per cent. solution (850 mEq per litre each of sodium and chloride) is employed and is injected slowly under close supervision since the too rapid intravenous injection of hypertonic saline causes cardiac arrest a 5 85 per cent. solution has the advantage that, being a molar solution containing a gram molecular weight of sodium chloride (58 5 g per litre) each millilitre of solution contains one milli-equivalent of sodium and of chloride and the regulation of the dosage is therefore much easier

SODIUM LACTATE.—A solution of sodium lactate is used to provide sodium without an anion, either when sodium deficiency

predominates, or by the addition of sodium lactate to another solution to increase the content of sodium in the resulting mixture. This provision of an excess of sodium, free of anion, is possible because the lactate is metabolised in the liver. Sodium lactate solution alone has a limited field of use to reduce the severity of the hyperpnoea in severe acidosis, for example in severe and advanced infection, but great care must be exercised in its administration An isotonic solution (one-sixth molar or 1·86 per cent.) contains 167 mEq. of sodium and lactate per litre

Potassium.—Potassium chloride is used in the treatment of potassium deficiency, due either to vomiting, when it is associated with alkalosis, or to loss of intestinal secretions, when there is usually an accompanying acidosis An isotonic solution of potassium chloride contains 1 11 per cent. potassium chloride (149 mEq potassium per litre), and this is too great a concentration of potassium for safe use By mixing equal parts of such an isotonic solution of potassium chloride with 5 per cent. glucose solution a safe concentration of potassium (74 mEq. potassium per litre or 0 55 per cent potassium chloride) is achieved. Alternatively, 20 ml of a 10 per cent. solution of potassium chloride are added to 500 ml of a 5 per cent solution of glucose to make a solution of 0 4 per cent potassium chloride (54 mEq. potassium per litre). In acute potassium deficiency 2 g. of potassium chloride (27 mEq potassium) may be administered by intravenous infusion during a period of 4 hours

Mixed Electrolyte Solutions—The solutions which have been described so far replace only water, one cation and one anion. By combining several salts in appropriate concentrations in a single solution it is possible to replace more accurately the complicated losses of electrolytes which are commonly incurred in clinical practice The best example of such a combination is the solution introduced by Darrow (1946), the beneficial effects of which in infantile gastro-enteritis have been described on p. 47

SALINE LACTATE (Hartmann's solution)—In this solution the excessive quantity of chloride in proportion to sodium in isotonic (0 9 per cent) saline is reduced by the addition of sodium lactate. It contains in one litre 6 0 g. of sodium chloride and 50 ml of molar sodium lactate solution (158 mEq sodium, 102 mEq chloride and 56 mEq lactate per litre). The same solution can be prepared by adding one volume of one-sixth molar sodium

lactate solution to 2 volumes of 0·9 per cent. saline (Darrow *et al*, 1949).

RINGER LACTATE.—This solution contains potassium chloride and calcium chloride in addition to the sodium chloride and sodium lactate in Hartmann's solution and is intended for use in patients with acidosis and potassium deficiency It contains too little potassium and rather more sodium than are desirable for the treatment of potassium deficiency

DARROW'S SOLUTION (K LACTATE) —This solution was originally introduced for the treatment of the losses of gastro-intestinal secretions in infantile diarrhoea When administered by intra venous infusion to babies Govan and Darrow (1946) recommended that the solution should be diluted with 5 or 10 per cent. glucose solution, but in adults this is not necessary It contains 4 0 g sodium chloride, 2·7 g potassium chloride and 50 ml molar sodium lactate per litre (124 mEq sodium, 36 mEq potassium, 104 mEq chloride and 56 mEq lactate per litre) This solution can be used in the treatment of potassium deficiency provided there is an adequate output of urine It was designed to correct extracellular fluid depletion (by the administration of water, sodium and chloride) as well as potassium deficiency and acidosis (by the administration of lactate) The potassium content of Darrow's solution is relatively low and its use is correspondingly safe, but the rate of administration should not exceed 1 litre in 4 or 5 hours. As soon as possible the oral administration of potassium salts should be started

Solutions containing magnesium and phosphate in addition to sodium and potassium chloride have been devised (Butler *et al*, 1946 Butler 1950 Fox *et al*, 1952) and represent a further advance in the replacement of lost constituents of intracellular fluid, but their value and the indications for their use are not yet certain. The main objective should always be the return to the consumption of a full mixed diet as soon as possible.

INTRAVENOUS INFUSIONS

To the patient an intravenous infusion is always a disturbing and often an alarming complication of his primary disease. Before an infusion is started, some explanation of the need and nature of the procedure should be given, and when complications arise, such

as leakage or thrombophlebitis, these also should be openly recognised, fully explained and promptly treated. An intravenous infusion should be continued for as short a period as possible. Immobilisation of the patient by the apparatus should be reduced to a minimum, and in this comfort and efficiency are closely linked.

Whenever possible the infusion should be administered through a needle inserted into an accessible superficial vein. Cannulation should rarely be necessary except in severely shocked patients. For the slow infusion of thin fluids, such as electrolyte or glucose solutions, fine needles are adequate, but when there is a possibility that more viscous fluids such as blood or dextran are to be employed, the widest-bore needle that can be inserted into the vein should be used. Melrose and Shackman (1951) have reminded us that doubling the diameter of the needle increases the rate of flow 16 times, whereas quadrupling the head of pressure on the fluid only doubles the rate of flow. It is also important to reduce the resistance to flow by ensuring that the narrow segments of the delivery set are as few and as short as possible. When polyethylene tubing is used instead of a metal needle or glass cannula, the length of the tubing should not exceed 6 inches unless concentrated solutions are to be injected into the great veins near the heart Even in children, Size 3 polyethylene tubing should be used whenever possible, since the rate of flow of blood and dextran is slow through Size 2; Size 1 is suitable only for 5 per cent. glucose or electrolyte solutions. Detailed instructions in the methods to be used in newborn and other children are given on p. 253.

To insert a metal cannula or polyethylene tube into a vein, the skin over the vein and the fatty tissue round the vein should be infiltrated with local anaesthetic, such as 2 per cent. Planocaine. Through a transverse incision ¾ inch in length the vein is then exposed and cleared for half-an-inch and two short lengths of 00 catgut are passed behind the vein, the distal ligature is tied, and one throw of a reef knot is loosely put on the proximal ligature. The vein is then opened between the ligatures by a transverse cut with small straight scissors which must be capable of cutting cleanly at the very tip of the blades. The cannula is then inserted into the vein and fixed by drawing the proximal ligature tight and completing the knot. The catgut ligatures are

cut short and the skin incision is closed with fine silk sutures. The use of catgut for tying the vein is more expensive than linen or silk, but allows the vein to reopen after absorption of the catgut.

Because of the persistent disability which may follow superficial thrombophlebitis of the internal saphenous vein the forearm veins should be used leg veins should not be used in patients who have abdominal or lower limb injuries intestinal obstruction, peritonitis or ileus The most useful vein of all is that which runs obliquely across the forearm from the lower end of the radius towards the middle of the cubital fossa and it is as constant in position as the internal saphenous vein When blood volume is low, this vein is not always easy to enter with a needle it is then better to insert a cannula this is also the wisest course to adopt in obese patients The large veins in the cubital fossa can nearly always be entered even with a large needle, but should be used only in emergency and for infusions of short duration the risk of damage to these veins and of displacement of the needle by movement of the arm is not entirely avoided even by firm splinting, which is uncomfortable When the cephalic vein in the middle of the forearm is used the forearm lies comfortably in pronation on the bed on a pillow and little fixation is necessary The veins on the back of the hand are not suitable for prolonged infusions, and leakage in this situation is particularly uncomfortable, and the bruising which follows leakage of blood after withdrawal of the needle is often very distressing to the patient and the relations

In severely shocked patients vasoconstriction markedly slows the rate of flow of fluid in the peripheral veins, and it is often an advantage to insert the needle for transfusion near the trunk. In general, the median cubital vein is the best for this purpose, but the internal saphenous vein at the mid thigh level may be an even better site. Although it lies largely beneath the deep fascia, its constant position makes the cephalic vein of value when the more commonly used veins have been thrombosed by infusions, the external jugular vein also may be used when others are thrombosed.

The introduction of disposable plastic tubing for intravenous therapy may slightly reduce the incidence of thrombophlebitis, when combined with plastic containers for blood the aseptic collection and sampling of blood and the separation of plasma and

cells are made much safer and easier. The storage of plasma for six months at room temperature to kill viruses is also easier and cheaper in plastic bags than in glass bottles, but this type of equipment is at present widely used only in North America.

The intravenous administration of concentrated (40 or 50 per cent.) solutions of glucose is now becoming commoner, the risk of thrombosis can be reduced, but not entirely avoided, if the solution is administered through polyethylene tubing into the superior or inferior vena cava. This tubing is inserted under local anaesthesia through an incision in the median cubital or internal saphenous vein and pushed in until the end of the tube has been advanced far enough into the chosen great vein. The tubing is then tied into the vein with a catgut ligature and should also be firmly fixed to the skin close to the incision, preferably by a silk stitch.

There are three main causes of stoppage of an intravenous infusion:

1. Damage to the vein wall by the sharp end of the needle. This is due to movement of the needle, usually because the needle has been inserted too near to a flexure or has not been properly fixed.

2. Displacement of the needle out of the vein—due to inadequate fixation.

3. Chemical thrombophlebitis—due to the irritation of the superficial veins by the infusion into them of 5 or 6 per cent. glucose solution. The irritation is due to the low *p*H of the glucose solution, which is reduced from about 6·5 to about 5·0 or even less during sterilisation by heat. The incidence of thrombophlebitis is closely related to the duration of the infusion and can be almost completely prevented by stopping the infusion of glucose after 8 hours. The skin overlying an affected vein becomes reddened and the wall of the vein becomes thickened and tender. When the veins of the leg are involved, a good deal of prolonged disability may result. It has been claimed without good evidence that the addition of a small quantity of heparin to the glucose solution prevents thrombosis.

CHAPTER XI

DISTURBANCES DURING INFANCY AND CHILDHOOD

DURING childhood and especially infancy disturbances of fluid and electrolyte balance are much less common though usually more critical, than in adult surgical patients In the newborn period while the causes and the effects of such disturbances resemble those in older children and adults, the structural and functional peculiarities, especially of the premature baby are so considerable that diagnosis, assessment and treatment must be based on different standards to those used after the first few months of life Even now our knowledge of these differences in structure and function is incomplete and treatment has remained largely empirical The newborn of all species have their own biological limitations and peculiarities and it is not enough simply to regard the newborn baby as just a little adult and to scale down adult treatment quantitatively on a weight basis without allowing any qualitative differences.

Disturbances of fluid equilibrium are relatively easier to produce in infants and may cause severe functional disturbances Interference with the intake of food the requirements for growth and a high metabolic rate, combined with differences in the internal environment and in the functions of the kidneys, and perhaps the pituitary and adrenal glands make the physiological background to losses by vomiting and diarrhoea very different to that found in adults and older children In this chapter some consideration must be given to what is known of these various aspects of neonatal physiology

BODY COMPOSITION

During the first week of life there are large changes in body composition which are related to the establishment of an independent existence. Often it is not recognised that other very large changes in the make up of the body have been going on in the uterus which are of particular importance in the surgical treatment of premature children.

Fat Content.—By the analysis of whole bodies Widdowson and Spray (1951) showed that the water content of the fat-free tissue of the foetus fell from over 90 per cent. at a weight of 200 g to 81 to 84 per cent. at more than 3 kg The fat content at birth weights of more than 3 kg. was from 12 to 16 per cent. of body weight, and this content of fat is about equal to that of protein It is remarkable that the human infant contains so much fat at birth since most newborn mammals contain only 1-2 per cent.; the high content in the human baby enables it to maintain a more stable body temperature and to have greater individual independence, both of advantage in single births. The premature baby weighing only 1 5 kg (3·3 lb.) contains only one-eighth the quantity of fat it would have at full term, and being less well insulated is more vulnerable to cold

Water Content.—The increasing fat content during the last half or third of pregnancy is related to the reduction in water content from 82·5 per cent. of body weight at 1 5 kg., to 77 per cent. at 2·5 kg., and 68 8 per cent at 3·5 kg. (7 lb.). Camerer *et al.* (1902) by desiccation found six newborn children to vary in water content from 69 2 to 73 0 per cent of body weight, with a mean of 71 8 per cent. Flexner *et al.* (1947) reported the mean water content of three normal newborns to be 74 6 per cent. Friis-Hansen *et al.* (1951), using antipyrine and heavy water simultaneously, reported a range of 70 2 to 83 per cent. in neonates and found that premature babies lay within the same range as full-term children. Edelman *et al.* (1952) also found similar high values in the first month of life, ranging from 71·6 to 83 per cent (mean 76 7 per cent.) During the first six months after birth the body water content falls to about 60 per cent. of body weight, at which it remains regardless of sex until puberty.

To be of any value clinically a method for measuring directly the total water content of a baby should have so small an error dependent on the physical or chemical methods used, that the total errors of the method are less than the change in water content which is expected to have occurred between measurements. For example, Friis-Hansen *et al.* (1951) found that when they used a micro-method for serial analysis of antipyrine in capillary blood, the cumulative errors were so large that in the case of a baby weighing 4 kg (8 8 lb), with 3 litres of body water, only a

change of 250 ml or more (8 per cent) in body water was significant. With smaller changes in water content they achieved a higher degree of accuracy with one estimation of antipyrine combined with serial weighings and the complete collection of urine.

It must be recognised that there are wide variations in body composition between individual newborn infants, due for example to differences in the size of the skeleton and thus in the proportions of bone and soft tissue as well as in fat content, and that infants with the same body weight do not have identical daily requirements for calories water or minerals or present exactly the same therapeutic problems The methods at present available for the measurement of total body contents of water sodium or potassium are subject to such errors that single estimations must be interpreted with very great care when they are employed in small babies The use of so-called standard values for the calculation of these body contents from the weight is also liable to be misleading although it is the only way in which most clinicians can obtain any idea of the normal range of composition of their patients.

Distribution of Water.—The distribution as well as the total quantity of water in the body undergoes a series of changes with increasing age Fellers *et al* (1949) measured the extracellular fluid volume and found that it decreased rapidly during the first weeks of life and again at adolescence. At birth weights of 2 to 5 kg the extracellular fluid was equal to just over 40 per cent. of the body weight and fell to 32 to 35 per cent. at body weights from 5 to 20 kg and to 23 to 27 per cent in adults Thus in the newborn the extracellular fluid volume is in proportion nearly 80 per cent. larger than in an adult, and this is of course associated with a smaller proportion of cellular material in the infant than in the older child or adult. The intracellular fluid amounts to only about 30 per cent of body weight in the newborn, compared with over 40 per cent in adults, and the total solids of the newborn equal about 20 per cent. of body weight instead of 30 per cent. in the adult (Table XXVI) These variations are associated with differences in sodium and potassium content at birth per kilogram body weight the sodium content of the body is 50 per cent. higher and the potassium content is 20 per cent lower than in adults (Table XXVII)

TABLE XXVI

	3 5 kg Newborn		*70 kg Adult*	
	% body weight	*litres*	*% body weight*	*litres*
Water content	70	2·5	60	42
Extracellular fluid	40	1·4	17	12
Intracellular fluid	30	1 15	43	30

Table to show the percentages and volumes of total body water, extracellular fluid and intracellular fluid in the newborn child weighing 3 5 kg. and the typical adult male weighing 70 kg

TABLE XXVII

	3·5 kg Newborn		*70 kg. Adult*	
	Sodium	*Potassium*	*Sodium*	*Potassium*
Extracellular fluid	189	7·0	1680	60
Intracellular fluid	17	128	300	3360
Total	206	135	2070	3420
Ratio	1 5		0 6	

Table to show the theoretical distribution of sodium and potassium in the extracellular and intracellular fluids of a newborn child weighing 3 5 kg and the typical male adult weighing 70 kg The sodium and potassium content of bone has been ignored and total quantities have been calculated from the same concentrations as used in Table (IV) and from the volumes given in Table (XXVI).

WATER BALANCE

A large loss of weight, amounting to 10 per cent. or more of birth weight, is a constant feature of the first few days of life. In full-term infants this loss of weight is related to the duration of the restriction of water intake and can be reduced by starting the water intake soon after birth. Premature infants may lose 20 per cent. or more of their birth weight without apparent harm and lose more water, sodium and potassium in larger daily volumes of urine for longer than do full-term babies.

Insensible Water Loss.—When a 3 5 kg. (7 lb.) baby loses 10 per cent (350 g.) of its birth weight in 3 or 4 days, only 20

to 30 per cent. (70 to 105 ml) of this loss can usually be accounted for by the quantity of urine which is passed during this time Some of the remainder is due to the consumption of tissue to provide for the continuing energy requirements of the body, but the bulk of the lost weight is caused by the insensible loss of water in the expired air and through the skin While the rate of insensible water loss may be influenced by the temperature and humidity of the environment, there is reason to believe that as in adults, the insensible water loss (p 18) is responsible for the dissipation of about 25 per cent of the total heat production of the body (Levine and Marples 1930) At an energy consumption of 60 calories per kilogram per day (Butler and Talbot 1944) an infant weighing 3 5 kg would metabolise 210 calories per day and this would impose on it an insensible water loss of 90 g per day a figure which conforms well with the results of clinical observations McCance *et al* (1954) found that the average extrarenal water loss of ten babies was 1 15 g per kg per hour or about 96 g per 24 hours, and Benedict and Root (1926) estimated the hourly loss might be as high as 1 3 g per kilogram or 109 g per 24 hours for a 3 5 kg child If it were easier to measure the caloric consumption or heat production insensible water loss could be calculated from such data but it is much easier to collect the whole output of urine faeces and any other losses from the body and to weigh the child accurately and thus to arrive at a reasonable estimate of insensible water loss plus the weight of tissue consumed for the provision of energy

Temperature Regulation.—To a varying extent the newborn baby is at the mercy of its environment. The young of some species, such as mice and rats are poikilothermic and as they cool their oxygen consumption and heat production fall Thus they have no inherent capacity to maintain body temperature and must huddle together or against the body of their mother if they are not to lose heat so rapidly that they will cool too much and die. Puppies and kittens also have little control over their body temperature at birth, but newborn pigs are homeothermic and cooling stimulates their metabolism so long as they are fed The newborn baby also is homeothermic and its greater size also gives it an advantage over many small mammals, since the surface area of bodies of similar shape vary inversely with their size Only about 25 per cent. of the total loss of heat from the surface of the human

that at a temperature of 31° C. and 100 per cent. relative humidity insensible water loss was about half that of babies in room air. There is no evidence that a high environmental humidity has any effect apart from reducing the heat loss from the body possibly by diminishing the gradient for insensible water loss, although it has been speculated that respiration also is made easier. Theoretically there is a limit to the degree to which environmental humidity can be raised without causing hyperpyrexia, and it may be fortunate that it is seldom possible to achieve 100 per cent. relative humidity in incubators in clinical use An atmosphere of low relative humidity is most commonly encountered during winter in continental countries with extreme ranges of temperature, but in a temperate island climate such as that of Great Britain it is rather uncommon.

Water Requirements.—The recommended theoretical water requirements for infants vary even more widely than do those for adults and it is particularly unfortunate that so little attention or recognition has so far been given to the effects of climate on the real daily requirements for water. These arbitrary estimates of water requirements have usually been based on calculated surface area or on body weight. The possible error in calculating surface area has already been mentioned (p. 237) and compares very unfavourably with the error in weighing a baby, provided a few elementary precautions are observed. Each time the child should be weighed in the same type of clothing or covering before being fed. An error of one ounce in 10 lb. amounts to only 0·6 per cent The range of daily requirement is commonly too wide Oliver *et al.* (1958) suggested an allowance of 60±15 ml. per pound body weight per day; for a 10 lb baby this amounts to a variation of 300 ml. over a range of 450 to 750 ml. They suggested that this allowance be applied to babies weighing from 5 to 22 lb. (2 to 10 kg), but a variation of 150 ml. over the range of 225 to 375 ml. at a weight of 5 lb. seems too large.

RENAL FUNCTION

In spite of much individual variation during the first week after birth the volume, specific gravity and osmolarity of the urine follow a fairly consistent pattern. Urine present in the bladder at the time of birth which has been produced before birth is invariably

dilute, the urine passed during the first day of life usually includes a large proportion of this antenatal urine, and is usually of larger volume and more dilute than urine produced during the next two days. The volume of urine is only about 20 to 30 ml per day on the second and third days of life, but then begins to increase and may reach 120 to 150 ml by the seventh day Even when breast milk is fed from the first day, Thomson (1944) found that only small quantities of urine were passed on the second and third days. Before birth urine osmolarity is about 50 mOsm per litre and rises to 400 to 500 mOsm. per litre during the first three days after birth and falls again to about 100 mOsm as the water intake rises at the end of the first week (McCance, 1950)

Hansen and Smith (1952, 1953) compared the effects of giving and withholding water during the first three days after birth. They found that when water was withheld the weight loss was greater and urinary volume was smaller the total losses of sodium and chloride in the urine did not vary although those of potassium and nitrogen did, and the serum concentrations of sodium and chloride and the haematocrit rose. They compared these changes with those in adults treated in a similar way and showed that the losses of weight and water were similar whether water was given or withheld With an ample water supply the losses of sodium potassium and other ions were less in full-term or slightly premature infants than in adults the newborn infants losing only a quarter as much sodium and potassium expressed per litre of body water as an adult or a baby more than a month old. One of the most remarkable features of renal function during the first week of life is the remarkable capacity of the kidneys of the newborn to restrict the excretion of sodium and potassium in the urine which falls to levels of less than 20 mEq per litre of urine within 48 to 72 hours of birth

Although the kidneys in the newborn cannot concentrate urine to the degree which is achieved later in life, and this imposes a larger loss of water in the urine than is necessary in older subjects, there is a good deal of evidence to show that renal conservation of sodium and potassium is usually very efficient even during the first week after birth. This adds to the interest and significance of the effects observed when the newborn premature or full term infant is loaded with water or saline. Lasch (1923) showed that during the first month of life infants could excrete only 55 per

cent. of a water load; the remainder was only partly accounted for by extrarenal losses and in spite of the retention of water the rate of urine formation fell. McCance *et al* (1954) gave infants 6 to 18 days old a dose of water equal to 6 per cent. of their body weight and found that urinary volume rapidly increased to a degree comparable to that in adults, provided the volumes were compared on the basis of 42 litres of body water. At the peak of the diuresis glomerular filtration rate and tubular reabsorption were very similar per unit of body water and the urine was as dilute in infants as in adults loaded to a comparable degree. The infants, however, could not excrete within four hours as the adults did, a volume of urine equal to the dose of water.

The urine of infants is hypotonic compared with that of older children and their renal clearances of urea, sodium, potassium and chloride are always low even when plasma concentrations are raised. Glomerular filtration rate and renal clearances rise during the first year to reach adult levels after 12 to 18 months, but vary widely between individuals and with hydration (McCance and Young, 1941).

In spite of some obvious limitations, the range of function of the infantile kidneys is clearly adequate for the peculiar circumstances of normal neonatal life. When, however, large quantities of glucose solution or saline are administered, especially by intravenous infusion, the limited capacity to excrete a water load and the low renal clearances of sodium and chloride may lead to the retention of undesirably large quantities of such fluids At present too little is known of normal function during the first month of life, as well as of the effects of operation on metabolism and growth, for specific treatment to be prescribed for each individual, and too often at the best only routine calculations are made from arbitrary estimates of average functions. It is always difficult to decide exactly how much water, minerals and calories should be given to each child, especially during the neonatal period when the margin between enough and h is so small.

adult pattern of response is acquired early during the first year of life, and often within two or three months of birth, although what is regarded as full maturity of renal function, the attainment of the adult range of clearance and concentrating capacity, is not reached until the age of a year or eighteen months. During the birth of a baby a varying amount of injury is inflicted and when the effects of a surgical operation are added the original pattern is modified. It is as yet very difficult to describe in detail a normal range of urinary composition for the newborn child with the modifications imposed by different degrees of prematurity or post-maturity and the exact length of gestation is often in doubt. Until a reliable means of dating every pregnancy is obtained, some doubt about the exact age of the child at birth must remain and it will be necessary to allow for a wider range of normal than is really desirable.

In a normal full term baby the urine volume falls rapidly during the first day, remains small for three or four days and then increases to about 120 to 150 ml per day by the end of the week, provided the consumption of water and milk is started The first urine passed after birth which has been formed in utero contains less than 50 to 60 mEq per litre each of sodium and potassium, the sodium usually being at a somewhat higher concentration than potassium Thereafter the concentration of potassium is usually higher than that of sodium, but the level of both falls to reach 5 to 10 mEq per litre on the fourth to sixth days.

When the effects of an operative injury are added within two or three days of birth the decline in urinary sodium and potassium concentrations may be delayed for a day or two and the very low concentrations may persist for several days longer than in the normal, the urine volume also may be low for more than the usual three or four days. It is very important to recognise that the kidneys of a newborn child which can reduce the concentration of sodium from around 140 mEq per litre in glomerular filtrate to less than 10 mEq per litre in the urine as passed from the fourth to the seventh to tenth days after birth are highly efficient. These kidneys excrete little potassium until some time after the intake of milk is started, but whenever an excessive potassium load is added to the body, are capable of responding by excreting potassium at a concentration of up to 50 or 60 mEq per litre. Rickham (1957) did not obtain evidence that there was

any urinary loss of potassium in excess of nitrogen after operation on neonates, or that the increase in urinary nitrogen output was greater after operation than during starvation. It is possible that tissue catabolism occurs in spite of the absence of any measurable increase in the urinary output of the products of breakdown of protoplasm, which may be explained by the utilisation of these substances for growth, an assumption which implies that both anabolism and catabolism occur simultaneously in different sites in the body. The marked potassium retention which is so common a feature of balance studies in the newborn is an indication of the rapid incorporation of potassium in the growing body, but even the newborn possesses enough renal functional capacity to protect the cells from too large additions of potassium to the cellular environment.

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insensible water loss and urinary output of the ba ere infused. Since it is known that the newborn tolerates well the restriction of water intake, and excretes very little sodium or potassium for some days after the first day of independent life, the object of post-operative treatment should be to establish oral feeding as soon as possible and to avoid the use of intravenous infusions. Nevertheless, when acute losses of water and sodium occur, the surgeon should be ready to employ the rapid infusion of an adequate volume of 0 9 per cent. saline without hesitation.

The slow continuous intravenous infusion of hypotonic saline and glucose is too often employed as a placebo for those in charge of the patient and in the newborn, particularly in those with congenital cardiovascular lesions, this can be lethal. Even when the

drip rate is reduced to 4 drops (0·25 ml.) per minute, which is as slow as can ever be reliably maintained and is seldom consistently achieved, 360 ml. will be delivered in 24 hours which is far more than most newborn children need. An infant weighing 3·5 kg. (7 lb.) with an insensible water loss of 90 ml. and a urinary output between 30 and 100 ml. per 24 hours is losing 120 to 190 ml. water per day. The common belief that babies need 2½ oz. water per pound body weight per day (165 ml. per kilogram) does not apply to the newborn; on this scale the 3·5 kg. infant would receive 500 ml. per day. Gross (1953) wisely recommended that the total intake of fluid in a premature baby should not exceed 30 ml. per pound per day (66 ml. per kg.) and that if this fluid were being injected subcutaneously or intravenously it

...ven in two or three parts at intervals of 12 or 8 hours.

...r cent. glucose solution and of a mixture of ...cose and 0·18 per cent. sodium chloride has ...because the glucose provides calories. 200 ml. ...ose solution will provide only 10 g. of glucose ...n cannot do more than take the edge off the ...n spare a little protein and help to make the ...nore complete. *The newborn baby weighing* ...tains about 128 mEq. of potassium in its 1·15 ...lar fluid and about 190 mEq. of sodium in ...cellular fluid. *There are 153 mEq. each of* ...ide in one litre of isotonic (0·9 per cent.) saline ...h in a litre of 0·18 per cent. (one-fifth normal) ... it may seem that a solution containing only 0·18 per cen... dium chloride confers an admirable degree of safety when used for infants, the dangers in administering the accompanying large volume of water have already been emphasised. The differences in volume, concentration and detailed composition between the fluid lost from the body and hypotonic saline, which the adult may tolerate without much harm during arbitrary therapeutic replacement according to formulas, are too often more than the infant can survive.

EFFECTS OF LOSS OF BODY FLUIDS

In children as in adults loss of gastro-intestinal secretions is the commonest and most important cause of disturbance of body fluid

equilibrium. During infancy accidental injury is a rare cause, and although gastro-enteritis is common it also only rarely is a complication of surgical treatment. The loss may be due to vomiting of gastric secretions in pyloric stenosis, of mixed gastric and intestinal secretions in intestinal obstruction due to atresia or stenosis of the intestine or to volvulus or incarceration of the small intestine in a hernia, or as the result of accumulation of intestinal secretions in the dilated bowel above an intestinal atresia or in ileus due to peritonitis or operation. The most important components of the lost fluid are sodium and water The concentration of sodium in the vomited or aspirated fluid varies from 100 to 140 mEq per litre, depending on the amount of water which has been drunk and the origin of the secretions The fluid thus resembles extracellular fluid in its sodium content, and if sufficient is lost the volume of extracellular fluid, and therefore also of the plasma, falls enough to cause an evident acute circulatory disturbance. Because the normal intake of water and milk and other food-stuffs also is hindered, the patient cannot replace the substances lost by vomiting. In the newborn child starvation is usually tolerated well for up to a week provided blood volume is maintained if necessary by transfusion during or after operation, and sufficient water and sodium are supplied by infusion to prevent any severe reduction of extracellular fluid volume. When interference with the normal intake of food persists for more than a week it is necessary to provide calories as fat and glucose and some form of protein, either as plasma, a hydrolysate or a solution of synthetic amino acids, as well as sufficient water, sodium and potassium salts and vitamins.

Clinical Features.—As in adults an accurate history is of primary importance and particular attention should be paid to details of the type and quantity of fluid which has been lost, as well as to the other features of the illness. At first the child frets and is wakeful, thirsty and has a dry tongue and red lips, but the eyes and fontanelle are not sunken and skin turgor is not much altered. As the loss of fluid continues, the child becomes obviously ill, pale, restless and anxious, the eyes and fontanelle are sunken, the lips are pale and may be bluish and the hands and feet are cold and blue although the rectal temperature may be raised. Blood pressure is usually maintained until a late stage even when

the pulse rate is raised but this circulatory compensation may be disturbed by sudden changes in position and unskilful handling of the baby When water depletion predominates, thirst is intense, the lips and tongue are cracked and dry and only a small amount of urine is produced

Until a baby is dead there is always hope and even when the child is mute, ashen grey with dull eyes deeply sunken in their sockets, and pulseless with cold, greyish blue hands and feet, a determined attempt should immediately be made at resuscitation, the astonishing response such an apparently moribund infant will make to the rapid intravenous administration of a suitable fluid is too often not appreciated or given an opportunity

It is no easier to measure changes in cellular composition or in extracellular fluid volume in ill babies than it is in adults, and chemical analysis of the blood provides information only of the concentrations of the constituents In babies it is necessary to use micro or ultra micro methods of analysis, especially for repeated determinations since the amount of blood which can be withdrawn is limited by the size of the child In an adult with a blood volume of 5 litres up to 20 ml of blood may be withdrawn for chemical analysis, but this is equivalent to only 1 to 2 ml in a neonate weighing 3 5 kg (7 lb) with a blood volume of 90 to 120 ml per kilogram An isolated estimation of any one constituent is not usually of much help because of the wide normal range in infancy The blood urea concentration in particular may be misleading in babies in whom it is normally high compared with the adult range, because of the low urea clearance rate in infancy high protein feeding, an inadequate water intake or a small reduction in renal function may each cause an elevation. In infants the plasma sodium concentration is usually within the normal adult range, but potassium is often considerably elevated and concentrations which in adults are believed to be incompatible with life are not uncommonly encountered in infants without apparent ill effects Smith (1951) has stated that the normal range for infants is up to 9 8 mEq per litre. Infants tend to become acidotic very readily with a high serum chloride and low bicarbonate and, as McCance (1950) has pointed out, this can be made worse by feeding fortified milk. The low rate of phosphate excretion by infants may reduce their ability to excrete organic acid in the urine, and this may account for their

greater tendency to become acidotic The infant may not be able to cope with ingested ammonium chloride as well as an adult, and this is an additional contra-indication to its use in pyloric stenosis with alkalosis. The infant has a limited capacity to vary the urinary *p*H The plasma protein concentration and the haematocrit are both high during the first three or four days of life, and during this period a sub-normal haemoglobin concentration is therefore an indication of a more severe degree of anaemia than usual Repeated estimations of the same constituents will sometimes provide worthwhile information of the rate and direction of a change in the composition of extracellular fluid, or perhaps an indication why current treatment is ineffective or is causing deterioration, but far more often the results of serum analysis are of less value in guiding and controlling treatment than close clinical observation

The complete collection of urine is difficult at any age and is only seldom possible in infants, but experienced nursing staff can make good estimates of changes in urinary output from the wetness and colour of the napkins Ideally, when a baby is losing gastro-intestinal secretions all the lost fluid as well as the urine should be collected, measured and analysed before a decision is made about the nature and quantity of fluid to be administered. Change in weight is more easily measured in small babies than at any other time of life and may give the best indication of the real size of the fluid losses which have been sustained. If changes in weight are to be properly interpreted it is necessary to think carefully about what factors are concerned in the particular set of circumstances. Interpretation is much more accurate when the volumes of the urine and other fluid loss have been measured, and changes in weight always include insensible water loss. When a fluid loss is continuing, the amount and direction of change in weight are very useful indications of the quantitative adequacy of fluid replacement, but when the weight of an infant does not change for several days the normal small daily increase in weight by growth should not be forgotten It is also very important to remember that, in acute intestinal obstruction and in some forms of chronic intestinal distension, fluid which is within the lumen of the intestine will be included in the body weight, although because of changes in the intestinal wall it is functionally lost to the body.

Causes of Disturbance in Infancy and Childhood

Only those causes which are peculiar to or have particular effects in children will be considered in this section

Oesophageal Atresia.—The consumption of fluid is prevented by the atresia, but when the diagnosis is made early and the obstruction is relieved by operation, the normal period of starvation after birth is increased by only a day or two until the administration of water and later milk is begun through a fine polyethylene tube passed across the anastomosis into the stomach Even when the diagnosis is made soon after birth broncho-pneumonia remains comparatively common following the inhalation of saliva which has overflowed from the proximal pouch. As in other neonatal emergencies an intravenous infusion should always be started just before operation but the rate of infusion should be limited to that necessary to maintain the infusion during operation in case blood transfusion is needed Blood loss at operation should be measured and should be replaced promptly if it is large enough but the degree of blood loss which can be tolerated varies according to the weight of the child There is seldom any need to continue the intravenous infusion after operation except when it is feared that a further transfusion may be needed and usually the infusion can be stopped the cannula in the scalp vein being closed off with a rubber cap

Neonatal Intestinal Obstruction.—Both *atresia* and *stenosis* are most common in the duodenum and ileum In atresia complete, and in stenosis almost complete, obstruction has been present in utero for some weeks, there is usually gross distension and hypertrophy of the bowel above the obstruction and vomiting begins soon after birth. The composition of the vomitus varies according to the level of the obstruction When this is above the ampulla of Vater the fluid is not bile-stained at lower levels abdominal distension is more common, but the proximal segment of bowel is always distended with fluid When atresia is not relieved by operation, the baby seldom survives for more than 7 to 10 days. Relief of the obstruction is the primary therapeutic consideration and should be deferred only to pass a soft tube and empty the stomach by aspiration and to restore blood volume by the transfusion of enough dextran or blood The infusion should be maintained during operation because the blood loss is often

large and the maintenance of blood volume by transfusion is an important factor in successful treatment. Attempts before operation to replace fluid lost by vomiting and into the lumen of the gastro-intestinal tract by the infusion of isotonic saline are unwise, because a large part of the injected saline passes into the obstructed intestine and makes its handling at operation more difficult. Unless the huge dilated segment immediately above the obstruction is resected before the anastomosis is done, there is delay in emptying after operation with persistence of abdominal distension, constipation and vomiting. As a result, gastric aspiration and intravenous infusion must then be continued for some days and recovery is less likely. Normally when an adequate resection and anastomosis are done aspiration can be stopped within a day or two of operation and oral feeding of dilute feeds can be started

Sometimes, especially when there are several atretic areas with isolated segments of intestine between them, or when after volvulus most of the midgut becomes gangrenous, only a short segment of small intestine remains after resection of the abnormal intestine. In such circumstances the food-stuffs subsequently pass through the short small intestine very rapidly and a feed is squirted out of the anus almost immediately after it is taken. As a result of this loss of both food and gastro-intestinal secretions the baby rapidly loses weight and condition. This problem requires a double approach. When the loss of body fluids reduces extracellular fluid volume, this must be corrected by the rapid intravenous infusion of isotonic saline, and loss of water insensibly and of water and sodium in the urine must be balanced by the infusion of a solution of 0 43 per cent. glucose and 0 18 per cent. sodium chloride. In addition, from time to time fat emulsion and human plasma may be needed to maintain the intake of protein and calories On the other hand the oral intake must be modified to provide as much readily absorbable food in a predigested state as can be tolerated and the passage of this food through the gastro-intestinal tract delayed by the use of tinct. catechu or tinct. opii or a chalk and opium mixture; a balance must carefully be struck between reducing the intestinal motility as far as possible without making the child so drowsy that he will not feed. In the early stages half cream or separated milk should be fortified with glucose and cornflour and predigested for 25 minutes, and later

an amino-acid solution and olive oil or coconut oil can be added

When *neonatal volvulus* is intermittent it is less likely to cause a severe circulatory disturbance than when a persisting tight twist leads to a closed loop obstruction and interference with the blood supply of a segment which may extend throughout the midgut. Volvulus is less common in the neonatal period than atresia. The addition of blood loss into the vessels, lumen and wall of the twisted segment causes circulatory failure at an earlier stage than in atresia, and transfusion is often needed before operation can be started.

Acute intussusception is probably the commonest acute abdominal emergency between the ages of two weeks and two years, although both the incidence and the mortality have recently fallen Diagnosis is made early in about three-quarters of the cases, and with rare exceptions only in the remainder are blood loss into the bowel wall and lumen and fluid loss by vomiting likely to cause so severe a disturbance that blood transfusion is necessary When resection is required it is usually also necessary to replace lost blood by transfusion.

Hirschsprung's disease may cause acute intestinal obstruction even during the first week or two of life, or later a type of acute abdominal crisis marked by gross distension, vomiting and the passage of copious and often offensive loose faeces There is a rapid reduction in extracellular fluid volume with acute circulatory failure resembling that found in some other forms of severe diarrhoea and requiring to be corrected by the rapid intravenous infusion of isotonic saline. This should be followed by laparotomy and colostomy when the aganglionic segment is short, or ileostomy when it extends proximal to the pelvic colon. In the absence of enteritis there is not usually any difficulty in managing either the ileostomy or the colostomy Unfortunately infection is not uncommon and causes very large losses of gastro-intestinal secretions from the stoma. It is usually necessary to replace these losses by the rapid infusion of isotonic saline followed by 0·43 per cent. glucose and 0·18 per cent. sodium chloride solution, to stop the oral intake of food and to give chlortetracycline or chloramphenicol combined with tinct. opii Similar measures are needed when Hirschsprung's disease is complicated by peritonitis with severe distension combined with vomiting and diarrhoea.

The diagnosis of acute intestinal obstruction due to incarceration of bowel in *inguinal* or *diaphragmatic hernias* is seldom so long delayed that significant loss of fluid occurs either by vomiting or into the lumen of the bowel. Strangulation or its surgical relief may cause the loss of so much blood that transfusion is needed. After reduction of a diaphragmatic hernia, abdominal distension may interfere with cardio-respiratory function, even when the affected loops of intestine have been emptied by suction, and intravenous infusion should be restricted to the absolute minimum.

Peritonitis may be associated with a large change in blood volume in infants as in older children and adults. Blood transfusion is of most value during or immediately after operative treatment and should not be followed by the infusion of solutions of glucose or glucose saline. Only when vomiting recurs or persistent ileus has led to prolonged gastric aspiration should a short infusion of a carefully judged volume of saline be used.

Congenital hypertrophic pyloric stenosis is usually diagnosed early and treated surgically and now seldom causes severe disturbance of the body fluids, but in a few patients for one reason or another repeated vomiting continues for several weeks. Such babies are shrunken, dry and quiet and may weigh less than at birth. It is important to recognise that while they have lost a large part of their extracellular fluid and that this can be acutely replaced by the rapid infusion of saline with marked improvement in their appearance and condition, a lot of fat and protein has also been destroyed during the period of vomiting and starvation, and this can be restored only by the feeding of milk. Moderate depletion of potassium can be readily corrected by starting milk feeds soon after operation. In the rare baby who is sleepy, inactive and limp even after the infusion an adequate volume of saline, potassium chloride up to a maximum of 5 mEq. potassium per kilogram body weight may be infused during 24 hours provided the urinary output exceeds 120 ml per 24 hours.

Pre-operative Treatment

Infants can be fed until four hours before deliberate operation, the last feed being of 5 per cent. glucose solution. Older children

should not drink for 4 to 6 hours before operation, but none should be purged. The complicated disturbances of body composition which result from prolonged illness and its treatment can be modified only to a very limited degree before operation, and in general a normal state is not restored for some weeks after a successful operation Severe malnutrition can be corrected only by the consumption of a diet suitable to the age of the child and containing enough protein calories, minerals and vitamins to enable lost tissue to be replaced in addition to the requirements for daily metabolism and growth.

Maintenance of Blood Volume—Newborn children tolerate even major abdominal and thoracic operations very well provided their blood volume is maintained To do this it is necessary to keep a close watch on the rate and total quantity of blood lost, and this is most conveniently done by weighing the discarded blood-stained swabs and measuring the volume of the blood in the sucker bottle. Blood may be transfused intermittently by the injection of small volumes (up to 10 ml) into the cannula of a scalp vein infusion and in small babies this is probably a more desirable and accurate method to use than continuous transfusion.

Post-operative Treatment

Unless the alimentary tract has been the site of operation, children should be allowed to drink suitably limited quantities of water fruit juice or milk as soon as they ask for a drink. After operations under local analgesia for pyloric stenosis, feeding should be started within 4 hours of operation Although after major abdominal operations there is a similar disturbance of gastric motility and absorption to that found in adults, it seldom lasts as long nor is it usually necessary to stop drinking for more than 24 hours after operation. Routine parenteral administration of fluid has no place in paediatric surgical practice and intravenous infusions should be reserved for the few patients who, as well as being unable to eat or drink, suffer large losses of body fluids If replacement is then to be exact, it is essential that the fluid which is being lost from the body and the urine should be collected the completeness with which this is achieved is directly related to the skill and adequacy of the nursing staff The volume and the sodium and potassium content of the collected fluids are measured

and used as a guide to treatment, and the replacements should seldom exceed the losses. Gastric aspiration through a fine soft polyethylene tube should be intermittent and should be stopped as soon as the fluid is clear and smells clean; the tube should be changed daily for cleaning, and drinking should never be allowed as long as aspiration continues.

It has been recommended (Williams *et al.*, 1949) that the intake of protein should be maintained by the transfusion of up to 1 0 g. per pound body weight of human plasma protein per day. So long as the intake of calories, apart from those derived from the plasma protein, is high enough to satisfy the basal daily energy requirements, this use of plasma is probably theoretically sounder than the use of solutions of hydrolysed milk protein, or of synthetic amino-acids, since it supplies whole protein in a form which is likely to be more readily and completely utilisable (*see* p. 219). This means that a 3 5 kg. (7 lb.) infant ought to receive in addition to about 150 ml. plasma containing 7 0 g. of plasma protein, 210 calories per 24 hours as fat emulsion and glucose. Such an intake can be provided as 160 ml. of 15 per cent. fat emulsion containing 4 per cent. glucose; in this quantity of emulsion there are 24 g. fat, or nearly 7 g. fat per kilogram body weight. It is not yet certain for how long such a large amount of fat can be tolerated by infants, although up to 5 g. per kilogram per day (120 ml. fat emulsion) appears to be metabolised satisfactorily (Wilkinson, 1959, unpublished data)

The daily transfusion of plasma has also been recommended to maintain the circulating plasma protein concentration which in children, as in adults, declines during the first week after operation. Since this decline is probably related in children also to post-operative protein catabolism, the transfusion of plasma alone without an adequate accompaniment of calories may not do much good. Water soluble preparations of vitamin B complex, ascorbic acid and vitamin K should be given by intramuscular injection every other day when oral feeding must be stopped for more than a week.

Control of Treatment.—Before treatment is begun it is essential to have a clear idea of the nature of the disturbance and of the kind of fluid loss which has caused it. A plan of treatment should then be made and reviewed and if necessary modified each time the state and progress of the infant are assessed, which in

acute illness should be at intervals of 6 hours. Oral and parenteral intakes and the output in stools, urine, vomitus or aspirations should be recorded hourly by the nursing staff It is essential that once every 24 hours all the data from preceding days of the illness are reconsidered A suitable allowance for the insensible loss of water must be included in the daily total of loss from the body

Methods of Administration.—*Subcutaneous infusions* should be used only for the administration of small quantities of isotonic solutions and are not of much value when extracellular fluid volume is so far reduced as to cause obvious signs of reduction in blood volume. The addition of hyaluronidase increases the rate of absorption of subcutaneous infusions. *Rectal infusions* are unreliable, especially in surgical patients in whom disorders of the gastro-intestinal tract are the commonest cause of severe fluid loss. Because of the risk of infection with resistant organisms and osteomyelitis the *intramedullary* route should never be used. *Intraperitoneal* injection can be employed when the intra-abdominal organs are not involved, but its clinical applications have yet to be fully assessed.

Intravenous infusion is the most reliable method, since it allows a greater control of the rate of administration and of the volume used than any other but its technique must be modified for use in small babies The insertion of a fine needle into the superficial veins of an infant is usually difficult and demands considerable skill and practice. In the limbs the veins in the back of the hand are usually more easily seen than any others. In the scalp, however the tributaries of the superficial temporal vein are usually readily seen even in small premature neonates, and with practice and a suitable needle, can be entered more easily than any others.

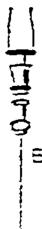
Technique of Scalp Vein Infusion.—The bottle and tubing should first be connected and filled with fluid. One half of the scalp is then shaved and cleaned with a 1 per cent. solution of Cetavlon. The baby is then laid across the cot in a good light and with the shaved side uppermost the head is held firmly in both hands by an assistant. The operator compresses the main stem of the superficial temporal vein just above the ear and chooses a suitable tributary A 21 B W G needle without a butt, 1⅜ inches in length and having a short bevel, is then held between the finger

and thumb or in a small artery forceps and pushed bevel upwards into the scalp over the vein and then obliquely down into the vein. A piece of 2D Portex tubing, 6 inches in length, is attached to the end of the needle and the blunt inner part of a Bateman cannula is inserted into the distal end of the Portex tubing (Fig. 12). When the needle enters the vein, blood flows along to the Bateman cannula to which is then connected to the adaptor on the end of the infusion set tubing. When the veins are constricted it may be necessary to use a finer needle (25 B.W.G.). The needle is then supported in a rigid bed, made either of wool soaked in collodion or of a small length of plaster of Paris bandage, which is held in position until it sets and then fixed to the head with several strips of half-inch adhesive plaster When a scalp vein infusion has been started before the operation begins, the anaesthetist is able to disconnect the Bateman cannula from the drip tubing and cover the cannula with a sterile rubber cap through which Pentothal and relaxant and other drugs may be injected. Blood also may be rapidly transfused in small quantities by removing the rubber cap and fitting a syringe on to the Bateman cannula.

During a prolonged intravenous infusion to ensure accurate control of the volume and rate of infusion a graduated cylinder should be included in the infusion system so that volumes of up to 30 ml. can be measured and administered over a period of several hours; the longer and narrower the graduated cylinder is, the more accurate the measurements will be. Unfortunately the head of pressure at the needle is reduced by the cylinder and flow may be irregular. Two types of cylinder are in general use, a short broad one 1 6 inches (4 cm.) in diameter and 4 inches (10 cm.) in length, and a long narrow one 0 75 inch (1·9 cm.) in diameter and 10 inches (25 cm.) in length, both graduated to 30 ml. (Fig. 12) When several solutions are being repeatedly administered it is convenient to connect the bottles by tubing to the inlet side of a three-way tap and have the burette below this tap and so be able to refill it from the appropriate bottle without disconnecting the bottles or tubing, this is especially important when fat emulsions and protein hydrolysates are being used. Dextran is too viscous to flow readily through a 25 B.W.G. needle and its value in the newborn is therefore rather limited unless a larger cannula or polyethylene tube has been inserted into a superficial vein in the forearm larger than can usually be found in







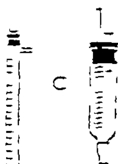


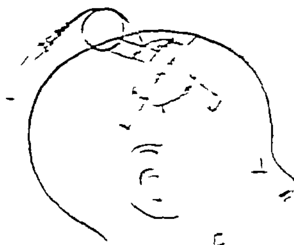
Fig. [illegible]

A. [illegible] B.T.G. needle without hub [illegible] in length, [illegible] of the end.

B. Inner [illegible] of [illegible] cannula which is inserted into [illegible] P[illegible] tubing, with adaptor for connection [illegible]

C. [illegible]

D. [illegible] needle and P[illegible] tubing [illegible]



the scalp. The technique of cutting down on a vein in an infant is the same as that used in adults (p. 228); local analgesia should always be used because this helps to reduce spasm in the vein, but it is usually difficult to find and to enter the fine vein amidst the subcutaneous fat of a baby's limbs.

APPENDIX I

Table XXVIII

The Normal Range of Concentrations of Blood Constituents

		mg./100 ml	mEq./litre
Serum	Sodium	316–340	137–148
	Potassium	15–20	3·8–5·1
	Magnesium	1·9–2·5	1·7–2·2
	Calcium	9·6–11·0	4·8–5·4
	Chloride	570–620 (as NaCl)	97–106
Whole blood	Chloride	450–530 (as NaCl)	77–90
	CO_2 combining power	52–72 (ml. CO_2)	
	Total bicarbonate		23–32
	Non-protein nitrogen	25–40	
	Urea nitrogen	9–16	
		g./100 ml.	mEq./litre
Serum	Total protein	5·5–7·6	13·4–18·5
	Albumin	3·3–5·3	
	Globulin	1·9–2·8	

Table XXIX

Atomic Weights, Valencies and Equivalent Weights

	Atomic Weight	*Valency*	*Equivalent Weight*
Sodium	23	1	23
Potassium	39	1	39
Magnesium	24	2	12
Calcium	40	2	20
Chlorine	35·5	1	35·5
Phosphorus	31	1·8	17·2
Sulphur	32	2	16

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Table XXX

Milliequivalents per Gram

1·0 g.	Sodium	contains	43·5	mEq	Sodium
,,	Potassium	,,	26·0	,,	Potassium
,,	Magnesium	,,	85·0	,,	Magnesium
,,	Calcium	,,	50·0	,,	Calcium
,,	Chloride	,,	29·0	,,	Chloride
,,	Sodium chloride	,,	17·0	,,	Sodium
			17·0	,,	Chloride
,,	Potassium chloride	,,	13·4	,,	Potassium
			13·4	,,	Chloride
,,	Sodium lactate	,,	9·0	,,	Sodium
			9·0	,,	Lactate

APPENDIX II

MILLIEQUIVALENTS

THE clinical convention that the concentrations of the constituents of body fluids should be expressed in milligrams per 100 ml. is still widely employed. This mode of expression describes the concentration of the individual constituents by weight but does not give any indication of their chemical activity The biological activity of any element depends largely on its chemical "equivalence or value rather than on its gravimetric weight. The universal chemical convention is to express concentrations in terms of the equivalent weights of the constituents of a solution by reference in this way to a common factor of equivalence, the hydrogen atom, it is possible to compare directly the chemical value or activity of different solutions and their constituents. The clinical importance of recognising alterations in the composition of body fluids is undisputed. Unless, however, the concentrations of the constituents of such fluids are expressed in terms of chemical equivalence, as milliequivalents per litre, the recognition and assessment of alterations in composition are made difficult and indirect.

The equivalent weight of an element is that quantity of it expressed in grams which is chemically equivalent to or will displace or react with, one gram of hydrogen. The equivalent weight is also equal to the atomic weight of the element divided by the valency The elements which are of clinical importance together with their atomic weights, valencies and equivalent weights are shown in Table XXIX. Most of these elements are monovalent in the case of phosphorus however within the normal range of *p*H of extracellular fluid, 20 per cent. of the phosphate is monovalent (BH_2PO_4) and 80 per cent. is divalent (B_2HPO_4) The valency of phosphorus in this mixed phosphate is therefore $0{\cdot}2+(0{\cdot}8\times0{\cdot}2)=1{\cdot}8$ Clinical convention has led to the expression of concentrations of bicarbonate ($BHCO_3$) and carbonic acid ($HHCO_3$) in terms of volumes of carbon dioxide per 100 ml. this figure can be converted to mEq /litre by dividing by 2 22

A milliequivalent is the equivalent weight of an element expressed in milligrams Milligrams can be converted to milliequivalents by dividing by the equivalent weight and vice versa. To convert a concentration expressed in milligrams per 100 ml. to milliequivalents per litre the first step is to multiply by 10 to convert to milligrams per litre. Milligrams are then converted to milliequivalents by dividing

by the equivalent weight; this is the same as dividing by the $\frac{\text{(atomic weight)}}{\text{valency}}$. For example

$$\text{mg. per 100 ml.} \times 10 = \text{mg. per litre}$$

$$\frac{\text{mg. per litre}}{\text{equivalent weight}} = \text{mg. per litre} \times \frac{\text{valency}}{\text{atomic weight}}$$

$$= \text{mEq. per litre}$$

For sodium

$$325 \text{ mg. per 100 ml.} \times 10 = 3250 \text{ mg. per litre}$$

$$\frac{3250 \text{ mg. per litre}}{\text{equivalent weight}} = 3250 \text{ mg. per litre} \times \frac{\text{valency}}{\text{atomic weight}}$$

$$= \frac{3250 \times 1}{23}$$

$$= 141 \text{ mEq. per litre.}$$

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